Assessing the Performance of Immunization Services in Sub-Saharan Africa: Timing and Completion Matters

by

Cara Bess Janusz

A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
(Epidemiological Science)
in the University of Michigan
2020

Doctoral Committee:

Professor Matthew L. Boulton, Chair
Professor Mousumi Banerjee
Assistant Professor Margaret Frye
Dr. Martin Mutua, African Population and Health Research Center
Assistant Research Professor Abram Wagner

Cara Janusz

cjanusz@umich.edu

ORCID iD: 0000-0002-1006-8135

Dedication

For my parents who inspire me to seek growth at any age, and always do my best – for others and myself.

Acknowledgements

I have many thanks and words of appreciation to share with the individuals and communities that supported me from beginning to end in my dissertation research. As I conclude this juncture of my life, first, I thank my chair, Dr. Matthew Boulton, for sharing his mentorship, rich experiences, knowledge, and trust in me, all of which helped me navigate the dissertation process and undoubtedly kept me focused on my big picture professional and academic goals of improving child health. Matt, your encouragement, and unwavering support during moments in which I questioned my place or direction were helpful in moving me onto the next step at each stage of this process. Thank you.

I am grateful to all members of my dissertation committee, Dr. Mousumi Banerjee, Dr. Margaret Frye, Dr. Martin Mutua, and Dr. Abram Wagner. Each of you found time to provide input, guidance, and mentorship to me during a period in the history of our careers and lives that is marked by so many unexpected demands. I appreciated every phone call, zoom, in-person meeting prior to covid, email discussion, even if there was no answer to be had, and most of all: getting to know you. I benefited tremendously from having your diverse experiences, disciplines, and interests contribute to my dissertation and growth as an epidemiologist and a researcher. I am especially thankful to Martin and his colleagues at APHRC for hosting and welcoming me in Nairobi.

While my time in the Epidemiologic Sciences PhD Program in some ways feels brief, I am thankful for having had numerous opportunities to interact with faculty during the first year of prelim coursework, summer seminar series, and other professional development activities. I prepare to leave the department having successfully done what I set out to do – grow my methodological skills and strengthen my research confidence – thanks to many in the department and my peers, who have taught me more than I could have ever anticipated.

Finally, I thank my family and friends who have supported me during my dissertation, and most importantly helped reorient my perspective when needed. To my sisters, Caitlin and Colleen, I am thankful for your constancy in all we do. To my parents, thank you for the visits

and invitations to escape my home office. To Pedrom, your presence encourages and inspires me. I am grateful to you, for all time.

Table of Contents

List of Tables

List of Figures

Abstract

Childhood vaccination coverage globally has increased since the launch of the Expanded Programme on Immunization in 1977 although delayed vaccination and failure to complete the recommended immunization series remains an important obstacle to the control vaccine-preventable disease. In sub-Saharan Africa, where >50% of the world's preventable deaths under-five years occur, research on the underlying mechanisms of under-vaccination is essential to realizing continued progress in eliminating preventable infectious disease-related morbidity and mortality in infants and young children. This dissertation explores drivers of vaccination disparities in sub-Saharan Africa, focusing on the competing programmatic priorities to innovate with inclusion of new vaccines while also urgently addressing under-vaccination against traditional disease targets.

In aim I, we assessed the prevalence of delayed childhood vaccination and its relationship with under-vaccination in the first year of life, pooling Demographic and Health Survey data from 33 sub-Saharan African countries conducted between 2010 and 2018. High prevalence of delayed vaccination (>24%) was found for all doses in the schedule, indicating children were vaccinated >4 weeks after the target age for effective coverage. Delays were strongly associated with incomplete schedules including failure to receive one or more vaccine doses by 12 months of age.

In aim 2, we examined the distal relationship between childhood death and immunization utilization patterns among surviving children. Using data from children and their decedent siblings across 33 SSA countries, we found that children with a prior decedent sibling had less

favorable vaccination outcomes compared to children who had no prior sibling death. Other measures of child mortality influence were considered at the province-level, which also showed less favorable vaccination outcomes for with surviving children in high U5M strata compared to lower ones.

Finally, in aim 3, we evaluated the temporal trends in adherence to age-specific vaccination recommendations in two informal settlement communities in Nairobi, Kenya. In this analysis, we compared trends between defined periods before and after the introduction of new vaccines in the basic immunization schedule using data from the longitudinal Nairobi Urban Health and Demographic Surveillance System between 2007 and 2015. We found no significant differences in the prevalence of delays between the two periods, suggesting no association between the introduction of new vaccines and the timeliness of delivering subsequent routine immunizations.

Together, this dissertation examined perspectives not previously considered on how underlying mechanisms inherent to immunization program delivery and prioritization influence overall progress towards aspirational goals for achieving effective coverage. By combining multiple measures, these studies contribute new ways of monitoring the performance of immunization programs in low coverage countries and informing the design of strategies to improve coverage in order to expand protection against vaccine-preventable diseases to all children.

Chapter 1 Introduction and Research Aims

Routine immunizations are among the most ambitious and effective initiatives to have ever been implemented for improving child survival globally. [1–3] The Expanded Programme on Immunization (EPI), launched by the World Health Organization (WHO) in 1977 following the successful eradication of smallpox through mass immunization campaigns, has led to remarkable declines in the global incidence of many common vaccine preventable diseases including diphtheria, tetanus, pertussis, Hepatitis B, *Haemophilus influenzae* type B, and measles.[4] Today, it is estimated that every year childhood vaccination prevents 2-3 million deaths worldwide and many more cases of illness and disability.[5] Despite these successes for childhood survival, there remain challenges to extending the benefits of immunization to all children. Childhood vaccination coverage in sub-Saharan Africa (SSA) is the lowest of any World Health Organization (WHO) region[6] while also experiencing the highest burden globally of under-five deaths associated with infectious causes, many of which are preventable with vaccination.[7]

In years following EPI's implementation in the WHO African region, the reach of immunization services increased from 5% coverage in 1980 to ≥50% of children receiving most commonly available vaccines by 2000.[6,8] Between 2000-2015, coverage with the 3rd dose of diphtheria-Tetanus-Pertussis (Penta3), often used to monitor the performance of routine immunization services within and between countries, increased from 52 to 71%.[6] However, in recent years, the pace of improvement has slowed or even reversed in some areas. By the end of 2015, across the whole of the SSA, only Rwanda had met the regional goal of vaccinating at least 80% of infants with DPT3 in all districts while most other SSA countries exhibited

uniformly low coverage.[9] In the following year, 2016, it was reported that 1 out of every 5 children in the region went without receiving any recommended life-saving vaccines (i.e. was non-vaccinated).[6] Additionally, survey-based research indicates that vaccination is often delayed for children who do have access to routine immunization services.[10] This dissertation contributes new perspectives for improving the reach of basic immunization services in SSA by evaluating both completion and timeliness of recommended vaccines. The research uses data sources commonly employed for the study of vaccination uptake, including cross-sectional assessment of vaccination status based on home-based records and parental recall, as well as longitudinal surveillance platforms installed to monitor health conditions for highly vulnerable populations. The specific research aims, and their hypotheses explored are as follows:

The **first aim** estimates the levels of delayed vaccination and under-vaccination across 33 sub-Saharan African countries using child-level vaccination records collected by Demographic Health Surveys between 2010-2019. Vaccination status for children at each age-specific recommended interval in the basic vaccination schedule was ascertained to examine associations between dose-specific delays and overall completion of the schedule. The hypothesis for this aim was that children frequently experience delayed vaccination, well after the recommended ages, and that these dose-specific delays in vaccine receipt would result in a lower likelihood of completing the basic immunization schedule by 12 months of age.

The **second aim** considers how the premature loss of a child under-five may influence vaccination patterns in other surviving children in the family and community by evaluating birth histories and vaccination records collected in Demographic and Health Surveys across 33 sub-Saharan African countries. The underlying exploratory hypothesis was that families who

experience a child death would have improved vaccination outcomes in subsequent children compared to families who do not experience such a life event.

The **third aim** examines whether the adoption of new vaccines, which add complexity to the basic schedule, shows any association with the timeliness of routine immunization services in two informal urban settlements in Nairobi, Kenya. Using data from the Nairobi Urban Health and Demographic Surveillance System, vaccination timeliness was evaluated over the period of 2003-2015 and then compared between the pre-introduction and post-introduction phases of new vaccine adoption in the Kenyan Expanded Programme on Immunization (KEPI). Considering that new vaccines introduced in this period were recommended for co-administration with other vaccines in the routine schedule, the hypothesis was that no abrupt changes to the timeliness of vaccination would occur when comparing the levels of delayed vaccination in the pre- and post-periods.

Background

The global landscape of immunization: challenges and opportunities in sub-Saharan Africa

WHO, member countries, and global donor partners have supported a massive scale-up of immunization services over the past fifty years.[11] With an estimated economic return of 16 times the required resource investment[12], continued strengthening of immunization services in low resource settings has even become a strategy for poverty alleviation in addition to improving childhood survival.[13,14] Since 1977, countries worldwide have used six basic antigens in their programs: Bacillus Calmette–Guérin (BCG), diphtheria-pertussis-tetanus (DPT), polio, and measles.[11] The delivery of these six antigens widely has led to the establishment of a global platform for disease elimination and eradication programs such as those targeting measles and polio, as well as more routine control of other traditional vaccine-preventable diseases and

diseases for which new vaccines have been developed.[11] The basic schedule of vaccines currently available to low- and middle-income countries has expanded to include vaccination against Hepatitis B, *Haemophilus influenzae* serotype B, rubella, mumps, pneumococcus, rotavirus, various meningococcus, and yellow fever in endemic areas.[15]

Immunization as a childhood survival strategy was central to making global progress towards the Millennium Development Goal (MDG) 4, which aimed to reduce under-five mortality by two-thirds between 2000 and 2015.[2] During these years, the Bill and Melinda Gates Foundation, governments, and other development assistance partners came together to establish Gavi, the Alliance, to help subsidize the introduction of new, costly vaccines and support modernization of outdated immunization delivery and vaccine storage systems in some of the world's poorest countries.[15] In parallel, WHO and its partners renewed ambitious goals for immunization programs with a major focus on both expanding the reach of immunization and the number of disease targets in the basic schedule through the Global Vaccine Action Plan (GVAP). The GVAP 2010-2020, endorsed by the World Health Assembly in 2012, sought to accelerate an equity agenda for immunization programs by calling on all countries worldwide to achieve 90% coverage with their programs at national level, and at least 80% coverage of all lower administrative reporting jurisdictions.[16]

Many high-income countries had met or exceeded the GVAP goals by the 1990s and early 2000s. Today, the focus of programs in these countries has now shifted to coverage maintenance amid growing sentiments of vaccine hesitancy and even increased refusal despite overwhelming evidence in support of the benefits of vaccination for child health.[16] By contrast, in sub-Saharan Africa and other lower-income regions, there was a substantial gap to close between the baseline reported vaccination coverage in 2010 and the aspirational goals proposed

for achievement during the decade.[17] For example, at baseline, 33 of 44 sub-Saharan African countries needed to substantially improve coverage to meet the GVAP goals.[6] Of these countries, 17 were in a position of needing to scale-up coverage of their immunization programs by more than 15%.[6] Over the past decade, while progress has been made in the sub-region, much of the incremental coverage improvements have stalled and, as of 2019, a number of countries remain 'off-track' by 20% or more in their coverage to meet the end of decade goals.[6,16,17]

For the global immunization agenda beyond 2020, ambitious plans are being discussed yet again to guide sub-Saharan African countries and others globally in the post-MDG era which is now framed by the Sustainable Development Goals (SDGs) 2030.[13] Inequities in the provision of all available vaccines and access to complete coverage is at the center of these discussion, particularly in the face of population growth, increasing rates of migration and urbanization, and serious concerns for the capacity or political will of governments to halt the spread of emerging diseases with other control measures complimentary to vaccination.[17] Under ideal implementation conditions, immunization systems would deliver all vaccines proven to be safe and effective to all children, and especially prioritizing any considered high-risk for vaccine-preventable diseases.[13] Although strict indicators for monitoring immunization performance are not made explicit in the newly proposed plans, there is an implicit emphasis on moving towards a measure of progress that helps identify under- and un-immunized populations and target interventions towards these populations to minimize their overall risk of vaccine-preventable disease acquisition and contribution to transmission.[13]

Measures for monitoring the performance of immunization programs and their impact on health

Vaccination coverage targets reflect assumptions about the proportion of individuals that would need to confer vaccine induced immunity to slow disease transmission and reduce the

overall burden of disease, otherwise known as the critical vaccination or herd immunity threshold.[18] While the exact threshold level depends on whether the goal is disease reduction or elimination, many geographic regions have adopted a vaccination coverage target that aligns with levels thought to be required for interrupting indigenous transmission of measles.[19] Measles is a highly contagious virus that is cited as resulting in 12-18 additional secondary cases per infection in a fully susceptible population.[20] Under these conditions, defined by transmission and contact rates, population immunity of 91-94% would be required to prevent the occurrence of secondary chains of transmission.[20] Achieving vaccination coverage at these levels and then sustaining it over time has proven to be an implausible goal for many settings during the implementation of the GVAP.[17] Instead, combining multiple measures to track the performance of immunization systems provides a better understanding of where and how to target resources and interventions, that may eventually lead to attaining the aspirational coverage goals at higher levels for disease control and elimination. This type of monitoring involves measurement of access, retention, and adherence over the course of the childhood immunization schedule at sufficiently granular levels of analysis to detect risk pooling.[21]

Childhood vaccination schedules in sub-Saharan Africa include, at minimum, administration of Bacillus Calmette-Guerin (BCG) at birth for the prevention of Tuberculosis; Pentavalent (Penta, or the 5-in-1 combination of Diphtheria-whole cell Pertussis-Tetanus [DwPT] + *Haemophilus influenzae* type B [Hib] + Hepatitis B [HepB]) and polio vaccines at 6, 10, and 14 weeks of age to prevent against the debilitating health impact of polio, Hib-associated disease, whooping cough, neonatal tetanus, and the acute and long-term effects of infancy acquired Hepatitis B; and at least one dose of Measles vaccine at 9 months age.[22–29] Additionally, vaccines to prevent rotavirus diarrheas and pneumococcal disease in young infants

have been available for some time now have been developed and adopted for routine use in the majority of SSA nations between 2005 and present.[15] These vaccines are administered concomitantly with other vaccines at 6, 10 and 14 weeks.[30,31]

Access to immunization is often defined as receipt of BCG at birth as the initial vaccine recommended in childhood schedules. Subsequently, in follow-up immunization visits, retention is evaluated by considering any missed doses over the course of a multi-dose series, i.e. doses 1, 2, and 3 of polio and pentavalent vaccines. Finally, adherence to specific timing intervals for vaccination is useful for more precisely predicting age-specific vaccination coverage and, by proxy, immunity and protection. Together, these measures provide a framework for estimating the effective level of coverage of the full immunization schedule, or the proportion of children who receive all vaccines according to recommendations and are therefore considered protected against the disease targets included in the local schedule.[32]

Methods and data sources for tracking immunization progress in SSA

The measures previously reviewed are often calculated from administrative reporting at health facilities and then aggregated up to higher jurisdictions to estimate vaccination coverage at varying levels: sub-national, national, regional, and global.[21] Using routine health information systems, these estimations often rely on consolidating paper-based report of the number of vaccines administered to any child in a given time period as the numerator, divided by the estimated target population for the reporting jurisdiction over the same period (i.e., number of live births).[21] The use of administrative reporting for the estimation of vaccination coverage can lead to substantial over-assurance of the assumed level of protection in the population if the denominator is under-estimated, which is a concern where birth registration is low or vital records systems do not have complete coverage of births and accurate capture of migration.[33]

The limited validity of these estimates is often apparent when reported as coverage of greater than 100%.[34] Another source of over-stating assumed protection is counting children older than 1 year of age in the numerator even though they were vaccinated well beyond the target age for coverage and protection.[21,33] While under-estimation of coverage is less of a concern for disease control implications, there are consequences for misallocating resources to areas that do not truly represent high-need or high-risk when these resources could be more useful elsewhere.

Recognizing limitations regarding administrative data, many immunization program managers and policymakers rely on survey-based research to track the individual child-level status of vaccination receipt, either longitudinally in small populations or cross-sectionally across larger populations at different time intervals.[33] Among the several surveys used to collect vaccination histories, the Demographic Health Surveys (DHS) and Multiple Indicator Cluster Surveys (MICS) are the most commonly used by countries and the WHO to validate or inform judgements about the quality of administrative reporting.[35] These survey programs use a multi-stage probability sampling scheme of households to estimate nationally representative health and demographic indicators. Of importance for cross-national benchmarking studies to evaluate progress towards regional or global health goals, these surveys are standardized in their design and implementation between countries.[36]

DHS has broader availability in sub-Saharan Africa than MICS for estimating vaccination outcomes and was used in the first two aims of this dissertation. Another source of emerging importance for estimating or validating measures for tracking immunization performance locally is the 40+ health and demographic surveillance sites (DHSS) established throughout urban and rural areas in several countries of sub-Saharan Africa.[37] These systems aim to provide timely data for health policy and decision-making in places where civil and vital

registries are lacking or weak by establishing continuous monitoring of births and deaths at a more local level than the government systems currently in place. One such DHSS was established in two informal urban settlement communities outside Nairobi, Kenya in 2002.[38] The African Population and Health Research Center (APHRC), based in Nairobi, Kenya, manages the system that has now tracked births, migration, and deaths in the Nairobi neighborhoods of Korogocho and Viwandani for nearly two decades.[39] This system, the Nairobi Urban Health and Demographic Surveillance System (NUHDSS), was used as the primary data source for the third aim of this dissertation.

Both the cross-sectional survey approach managed by DHS and the longitudinal surveillance project managed by APHRC collect information on vaccination histories for children under the age of five in all households included in their sample or census tracking, respectively. Using a combination of parental recall probing and review of home-based records, survey interviewers collect the status of receipt for each recommended vaccine dose in the basic immunization schedule, the date on which vaccine administration occurred, if available, and other data to characterize children and their caretakers.[40,41] These data sources have previously been used to describe vaccination timeliness and coverage of specific doses and the complete vaccination schedule, as well as evaluate child, caretaker, and community factors that are associated with vaccination outcomes in several settings in SSA.[42,43,52–54,44–51]

Barriers to improving timing and completion of immunization in children

Studying factors that characterize childhood vaccination outcomes has been a major focus of the research literature on immunization services, as evidenced by the number of published reviews of the peer-reviewed literature on the subject in low- and middle-income countries.[32,55–57] A recent systematic review of 48 peer-reviewed studies on the barriers to

childhood immunization in sub-Saharan Africa found a common set of both modifiable and non-modifiable factors repeatedly at the center of this literature.[58] Parental and provider knowledge gaps regarding the safety and effectiveness of vaccines, lack of caretaker trust in the health system, and limited access to short wait times or convenient vaccination clinic hours were among the most commonly identified barriers to vaccination when considering factors that could be modified with community education and outreach.[58] Other child, mother, and community factors were also commonly explored such as education, race/ethnicity, religious affiliation, household wealth, population density, child rank, and household living arrangements.[58]

Identifying factors that positively or negatively predict vaccination uptake is helpful for developing priority groups for strategic outreach, but often these studies have recycled the same set of known risk factors instead of (1) looking more closely at bottlenecks in the system, or (2) considering overlapping factors that drive disparities in coverage. This dissertation explores three themes that were identified as gaps in the literature on barriers to childhood immunization in SSA, with a particular focus on using multiple measures of immunization performance to more closely ascertain the potential effective coverage of immunization services and therefore impact on child health outcomes. First, the timeliness and completion of the basic immunization schedule is assessed in 33 SSA countries. These two measures of the performance of immunization services are evaluated jointly with the aim of determining the extent to which delayed or late vaccination is associated with overall completion rates. Timeliness and overall completion are two important measures for evaluating the performance of immunization programs and approximating the impact of immunization on child health. However, the research literature has treated them as separate areas of focus instead of two measures that are intrinsically linked. In a second research aim of this dissertation, risk-prioritization for targeting

immunization outreach activities, special campaigns, and educational resources is evaluated considering the experience of childhood death in families and communities. Previous research on the determinants of under-vaccination in children has not explored the effect of overlapping disadvantages experienced among families and communities who reside in areas that are characterized by low access to health services and high under-five mortality. This second aim considers how experiences with under-five death in the family and community influence vaccination patterns in their surviving children in the same 33 SSA included for the first aim. Finally, the third research aim examines whether innovation to the basic immunization schedule, by adding additional vaccines and expanding the number of disease targets for control of VPDs, has had any negative implications for the timeliness of routine immunization. Using the example of pneumococcal conjugate vaccine (PCV) introduction in Kenya, the timeliness of routine immunization was assessed before and after the adoption of PCV in two urban, poor communities in Nairobi. Together, the findings from these three research aims provide new perspectives on how the use of multiple measures of immunization performance could help re-focus resources to improve vaccination outcomes and child health in SSA.

References

1. Bonanni, P. Demographic impact of vaccination: A review. *Vaccine* **17**, 120–125 (1999).
2. Hinman, A., Orenstein, W. & Schuchat, A. Vaccine-preventable diseases, immunizations, and MMWR--1961-2011. *MMWR Morb Mortal Wkly Rep* **60 Suppl 4**, 49–57 (2011).
3. Rodrigues, C. M. C. & Plotkin, S. A. Impact of Vaccines; Health, Economic and Social Perspectives. *Front. Microbiol.* **11**, (2020).
4. Andre, F. E. *et al.* Vaccination greatly reduces disease, disability, death and inequity worldwide. *Bull. World Health Organ.* **86**, 140–146 (2008).
5. World Health Organisation. State of the world ' s vaccines and immunization. (2009).
6. WHO. *WUENIC Estimates, 2020*. https://www.who.int/immunization/monitoring_surveillance/data/en/ (2020).
7. Liu, L. *et al.* Global, regional, and national causes of under-5 mortality in 2000–15: an updated systematic analysis with implications for the Sustainable Development Goals. *Lancet* **388**, 3027–3035 (2016).
8. Arevshatian, L. *et al.* An evaluation of infant immunization in Africa : is a transformation in progress ? **031526**, (2007).
9. Mosser, J. F. *et al.* Mapping diphtheria-pertussis-tetanus vaccine coverage in Africa, 2000–2016: a spatial and temporal modelling study. *Lancet* **393**, 1843–1855 (2019).
10. Clark, A. & Sanderson, C. Timing of children's vaccinations in 45 low-income and middle-income countries: an analysis of survey data. *Lancet* **373**, 1543–1549 (2009).
11. Greenwood, B. The contribution of vaccination to global health: Past, present and future. *Philos. Trans. R. Soc. B Biol. Sci.* **369**, (2014).
12. Ozawa, S. *et al.* Return on investment from childhood immunization in low- and middle-income countries, 2011-20. *Health Aff.* **35**, 199–207 (2016).
13. World Health Organization. *Immunisation Agenda 2030: A Global Strategy to Leave No One Behind*. *World Health Organization* (2020).
14. Naimoli, J. F., Challa, S., Schneidman, M. & Kostermans, K. Toward a grounded theory of why some immunization programmes in sub-Saharan Africa are more successful than others: A descriptive and exploratory assessment in six countries. *Health Policy Plan.* **23**, 379–389 (2008).
15. Sambala, E. Z., Wiyeh, A. B., Ngcobo, N., Machingaidze, S. & Wiysonge, C. S. New vaccine introductions in Africa before and during the decade of vaccines – Are we making progress ? *Vaccine* **37**, 3290–3295 (2020).
16. Cherian, T. *et al.* Global Vaccine Action Plan lessons learned III: Monitoring and evaluation/accountability framework. *Vaccine* **38**, 5379–5383 (2020).
17. MacDonald, N. *et al.* Global vaccine action plan lessons learned I: Recommendations for the next decade. *Vaccine* **14**, 5364–5371 (2020).
18. Fine, P., Eames, K. & Heymann, D. L. 'Herd immunity': A rough guide. *Clin. Infect. Dis.* **52**, 911–916 (2011).

19. Fine, P. E. M. Herd Immunity : History , Theory , Practice. **15**, (1993).

20. Guerra, F. *et al.* The basic reproduction number (R0) of measles: a systematic review. *Lancet Infect. Dis.* **17**, e420-2428 (2017).

21. Dolan, S. B. *et al.* Redefining vaccination coverage and timeliness measures using electronic immunization registry data in low- and middle-income countries. *Vaccine* **37**, 1859–1867 (2019).

22. World Health Organization. BCG vaccines: WHO position paper-Recommendations. *Wkly. Epidemiol. Rec.* **93**, 73–96 (2018).

23. World Health Organization. Diphtheria vaccine: WHO position paper - August 2017. *Wkly. Epidemiol. Rec.* **92**, 417–435 (2017).

24. WHO. Pertussis vaccines: WHO position paper - September 2015. *Wkly. Epidemiol. Rec.* **90**, 433–458 (2015).

25. WHO. Tetanus vaccines: WHO position paper. *World Heal. Organ.* **92**, 53–76 (2017).

26. World Health Organization (WHO). Haemophilus influenzae type b (Hib) Vaccine: WHO Position Paper–September 2013. *Wkly. Epidemiol. Rec.* **88**, 413–428 (2013).

27. World Health Organization (WHO). Hepatitis B vaccines: WHO position paper - July 2017. *Wkly. Epidemiol. Rec.* **92**, 369–392 (2017).

28. WHO. Polio vaccines: WHO position paper – March, 2016. *Wkly. Epidemiol. Rec.* **91**, 145–168 (2016).

29. WHO. Measles vaccines: WHO position paper - April 2017. **92**, 205–228 (2017).

30. States, M., Strategic, W. H. O., Group, A., Who, A. & Le, E. Rotavirus vaccines WHO position paper: January 2013 - Recommendations. *Vaccine* **31**, 6170–6171 (2013).

31. World Health Organization. Pneumococcal conjugate vaccines: WHO position paper – February 2019. *Wkly. Epidemiol. Rec.* **94**, 85–104 (2019).

32. Phillips, D. E., Dieleman, J. L., Lim, S. S. & Shearer, J. Determinants of effective vaccine coverage in low and middle-income countries: A systematic review and interpretive synthesis. *BMC Health Serv. Res.* **17**, (2017).

33. Cutts, F. T., Izurieta, H. S. & Rhoda, D. A. Measuring Coverage in MNCH: Design, Implementation, and Interpretation Challenges Associated with Tracking Vaccination Coverage Using Household Surveys. *PLoS Med.* **10**, (2013).

34. Dunkle, S. E. *et al.* Limitations of using administratively reported immunization data for monitoring routine immunization system performance in Nigeria. *J. Infect. Dis.* **210**, S523–S530 (2014).

35. Dansereau, E., Brown, D., Stashko, L. & Danovaro-Holliday, M. C. A systematic review of the agreement of recall, home-based records, facility records, BCG scar, and serology for ascertaining vaccination status in low and middle-income countries. *Gates Open Res.* **3**, 1–21 (2020).

36. Fabic, M., Choi, Y. & Bird, S. A systematic review of DHS - data availability and utilization for research. *Bull. World Heal. Organ.* **90**, 604–12 (2012).

37. Ye, Y., Wamukoya, M., Ezeh, A., Emina, J. B. O. & Sankoh, O. Health and demographic surveillance systems: A step towards full civil registration and vital statistics system in sub-Sahara

Africa? *BMC Public Health* **12**, 1 (2012).

38. Beguy, D. *et al.* Health & Demographic Surveillance System Profile Health & Demographic Surveillance System Profile : The Nairobi Urban Health and Demographic Surveillance System (NUHDSS). 462–471 (2018) doi:10.1093/ije/dyu251.

39. Wamukoya, M., Kadengye, D. T., Iddi, S. & Chikozho, C. The Nairobi Urban Health and Demographic Surveillance of slum dwellers, 2002–2019: Value, processes, and challenges. *Glob. Epidemiol.* **2**, 100024 (2020).

40. ICF International. *Standard Recode Manual for DHS 6*. (2013).

41. Mutua, M. K. *et al.* Fully immunized child : coverage , timing and sequencing of routine immunization in an urban poor settlement in Nairobi , Kenya. *Trop. Med. Health* 1–12 (2016) doi:10.1186/s41182-016-0013-x.

42. Mutua, M. K. *et al.* Fully immunized child: coverage, timing and sequencing of routine immunization in an urban poor settlement in Nairobi, Kenya. *Trop. Med. Health* **44**, 13 (2016).

43. Rossi, R. Do maternal living arrangements influence the vaccination status of children age 12-23 months? A data analysis of demographic health surveys 2010-11 from Zimbabwe. *PLoS One* **10**, 1–19 (2015).

44. Ndwandwe, D. *et al.* Decomposing the gap in missed opportunities for vaccination between poor and non-poor in sub-Saharan Africa: A Multicountry Analyses. *Hum. Vaccines Immunother.* **14**, 2358–2364 (2018).

45. Ntenda, P. A. M. *et al.* Predictors of uptake of newly introduced vaccines in Malawi - Monovalent human rotavirus and pneumococcal conjugate vaccines: Evidence from the 2015-16 Malawi demographic and health survey. *J. Trop. Pediatr.* **65**, 287–296 (2019).

46. Hanson, C. M. *et al.* Enhancing immunization during second year of life by reducing missed opportunities for vaccinations in 46 countries. *Vaccine* **36**, 3260–3268 (2018).

47. Uthman, O. A. *et al.* Does it really matter where you live? A multilevel analysis of factors associated with missed opportunities for vaccination in sub-Saharan Africa. *Hum. Vaccines Immunother.* **14**, 2397–2404 (2018).

48. Boulton, M. L. *et al.* Vaccination timeliness among newborns and infants in Ethiopia. *PLoS One* **14**, 1–13 (2019).

49. Kriss, J. L. *et al.* Vaccine receipt and vaccine card availability among children of the apostolic faith: analysis from the 2010-2011 Zimbabwe demographic and health survey. *Pan Afr. Med. J.* **24**, (2016).

50. Masters, N. B., Wagner, A. L., Carlson, B. F. & Boulton, M. L. Vaccination timeliness and co-administration among Kenyan children. *Vaccine* **36**, 1353–1360 (2018).

51. Ntenda, P. A. M. Factors associated with non- and under-vaccination among children aged 12–23 months in Malawi. A multinomial analysis of the population-based sample. *Pediatr. Neonatol.* **60**, 623–633 (2019).

52. Acharya, P., Kismul, H., Mapatano, M. A. & Hatløy, A. Individual- and community-level determinants of child immunization in the democratic republic of congo: A multilevel analysis. *PLoS One* **13**, 1–17 (2018).

53. McGavin, Z. A. *et al.* Childhood full and under-vaccination in Nigeria, 2013. *Vaccine* **36**, 7294–

7299 (2018).

54. Mbengue, M. A. S. *et al.* Vaccination coverage and immunization timeliness among children aged 12-23 months in Senegal: a Kaplan-Meier and Cox regression analysis approach. *Pan Afr. Med. J.* **27**, 8 (2017).

55. Smith, L. E., Amlôt, R., Weinman, J., Yiend, J. & Rubin, G. J. A systematic review of factors affecting vaccine uptake in young children. *Vaccine* **35**, 6059–6069 (2017).

56. Sridhar, S., Maleq, N., Guillermet, E., Colombini, A. & Gessner, B. D. A systematic literature review of missed opportunities for immunization in low- and middle-income countries. *Vaccine* **32**, 6870–6879 (2014).

57. Favin, M., Steinglass, R., Fields, R., Banerjee, K. & Sawhney, M. Why children are not vaccinated: A review of the grey literature. *Int. Health* **4**, 229–238 (2012).

58. Bangura, J. B., Xiao, S., Qiu, D., Ouyang, F. & Chen, L. Barriers to childhood immunization in sub-Saharan Africa: A systematic review. *BMC Public Health* **20**, (2020).

Chapter 2 Vaccine Delay and Its Association With Under-vaccination in Children in Sub-Saharan Africa

Abstract

Introduction: Improving the timeliness and completion of vaccination is key to reducing under-5 childhood mortality. This study examines the prevalence of delayed vaccination for doses administered at birth and age 6 weeks, 10 weeks, 14 weeks and 9 months and its association with under-vaccination among infants in sub-Saharan Africa.

Methods: Pooling data across 33 sub-Saharan Africa countries, vaccination timing and series completion was assessed for children aged 12–35 months who were included in the immunization module of the Demographic and Health Surveys conducted between 2010 and 2019. Survey design–adjusted logistic regression modeled likelihood of not fully completing the basic immunization schedule associated with dose-specific delays in vaccination. Data were obtained and analyzed in May 2020.

Results: Among children with complete date records (n=70,006), the proportion of children vaccinated with delays by ≥1 month was high: 25.9% for Bacillus Calmette–Guérin (birth); 49.1% for the third dose of pentavalent (14 weeks) and 63.9% for the first dose of measles (9 months) vaccines. Late vaccination was more common for children born to mothers with lower levels of educational attainment (p<0.001) and wealth (p<0.001). Controlling for place, time, and sociodemographics, vaccination delays at any dose were significantly associated with not completing the immunization schedule by 12 months (Bacillus Calmette–Guérin: AOR=1.93,

95% CI=1.83, 2.02; pentavalent: AOR=1.50, 95% CI=1.35, 1.64; measles: AOR=3.76, 95% CI=3.37, 4.15).

Conclusions: Timely initiation of vaccination could contribute to higher rates of complete immunization schedules, improving the reach and impact of vaccination programs on child health outcomes in sub-Saharan Africa.

Introduction

Considerable progress has been made in reducing under-5 mortality, which globally has declined by 53% from 1990 to 2015.[1] Despite this success, progress in sub-Saharan Africa (SSA) has been slower: Only 8 of 43 countries in the region met or exceeded the Millennium Development Goals related to childhood survival by 2015.[2] Consequently, it is estimated that nearly two thirds of SSA countries will need to accelerate improvement in order to achieve the updated goal of reducing under-5 mortality to <25 deaths per 1,000 live births in every country by 2030 in line with the Sustainable Development Goals.[1]

Inequities in vaccination are a major contributor to disparities in childhood health and survival.[3,4] This is evidenced in SSA, where some of the highest rates of childhood mortality globally (>100 per 1,000 live births) coincide with less than one third of countries reporting immunization schedule completion in infants >60%.[5] The low rates of age-appropriate vaccination directly threaten progress made in the control and elimination of vaccine-preventable diseases (VPDs) that contribute importantly to improving childhood survival.[6,7] The WHO Expanded Programme on Immunization recommends that young children in most countries globally receive 1 dose of Bacillus Calmette–Guérin (BCG) at birth, 3 doses of oral polio vaccine (polio) and 3 doses of the pentavalent (penta) combination vaccine (i.e., diptheria-tetanus-pertusis, hepatitis B, *Haemophilus influenzae* type b) at age 6 weeks, 10 weeks, and 14

weeks and 1 dose of measles-containing vaccine (measles) at age 9 months.[8] These recommendations are adapted to address the specific epidemiological profile at the country level, but all countries in SSA at a minimum use this basic series and some may additionally offer newer childhood vaccines. To achieve effective control of VPDs, high rates of both timely receipt and completion of the basic schedule are needed. In acknowledgement of this, the WHO's Immunization Agenda 2030, which has put forth aspirational goals for national immunization programs in line with the Sustainable Development Goal agenda, underscores the importance of both receiving vaccination altogether but also ensuring that access to on-time vaccination is available to target the age-specific vulnerabilities children have for each VPD covered in the schedule.[9]

Previous studies on timeliness and completion of childhood vaccination in SSA have focused on underlying determinants, including spatial and sociodemographic factors associated with low uptake or poor adherence to age-specific vaccination recommendations.[10–15] However, no studies have evaluated the association between delayed vaccination and failure to complete the basic series by 12 months outside of high-income countries.[16,17] Delayed vaccination poses public health risks both in terms of disease acquisition for the individual as well as transmission in the community as children remain susceptible to and reservoirs for VPDs for unnecessarily prolonged periods of time.[18,19] In real time, the level and duration of risk associated with delayed vaccination is unknown because the visibility of vaccination timing is limited when relying on administrative data.[7] Across countries, vaccination coverage is estimated by aggregating reported administrative data on the total doses administered for each vaccine in the target population of surviving infants, estimated from census data, over a defined period of time.[20] These aggregate measures of coverage mask age-specific vulnerabilities, and potentially obscure patterns of

clustered risk that program managers and policymakers could address with a more granular view of adherence to age-specific vaccination recommendations.[7] Importantly, although a less commonly explored implication, vaccination delays may also increase the likelihood of missing subsequent doses, and even dropping out of the schedule before concluding the full series of vaccines in the first year of life, as is recommended. Understanding the extent to which vaccine delays occur across the schedule and defining the role that delayed vaccination plays in completing all recommended vaccines could help inform strategies that reduce bottlenecks to achieving full coverage of the childhood vaccination schedule, ultimately improving the effectiveness of vaccination and its impact on childhood survival. Using data from the Demographic Health Survey (DHS) conducted in 33 SSA countries, this study seeks to: (1) estimate the prevalence of delayed vaccination at specific vaccination encounters in the schedule and (2) explore the association between delays in dose-specific vaccination and the completion of the basic immunization schedule.

Methods

Study Population

Established in 1984, the DHS program collects nationally representative data on health and demographics using standardized survey designs across participating countries.[21] This widely used cross-sectional data source has been described in depth elsewhere.[22] All publicly accessible DHS surveys in SSA conducted between 2010 and 2019 were identified for this study, totaling 47 surveys from 33 countries (available as of June 2020 at www.dhsprogram.com/data/available-datasets.cfm). The sample was restricted to the most recent survey conducted per country (Table 2.1).

The DHS uses a multistage, unequal probability sampling scheme to identify a nationally representative sample of households.[22] At the first stage, household clusters are selected based on probability proportional to the population area size from each rural or urban strata, defined by the host country. Then, after creating a complete listing of households within the cluster, approximately 30 households are randomly sampled. All women aged 15–49 years who reside in the selected households are invited to participate in the survey.[23]

Vaccination data are collected for living children who were born in the 3–5 years prior to the interview.[24] Data from children aged 12–35 months at the time of interview were used in this study, as this age group consistently participated in the vaccination module across the countries selected for inclusion. Owing to the potential of correlated vaccination patterns among siblings, the sample was restricted to the youngest child in instances where multiple children from the same family were age eligible (excluding 3.2% of the age-eligible sample).

Mothers are asked to report on their children's status of receipt for each recommended vaccine in the national immunization schedule. To verify, interviewers review family health cards or children's immunization records, when available, to confirm the date of vaccination.[25] Dates recorded on the vaccination card were used to assess timeliness and series completion. Children who did not have a card available at the time of interview or who had a card without record of complete or plausible vaccination dates were excluded from analysis.

Measures

The primary outcome of interest was completion of the recommended immunization schedule in the first year of life. All analyses used complete vaccination series status as the reference level. Incomplete vaccination schedules were defined as lacking any dose in the 8 basic

dose series, which includes BCG at birth, 3 doses each of penta and polio at age 6, 10, and 14 weeks, respectively, and 1 dose of measles at age 9 months. Dose-specific vaccination timeliness was explored by creating a 3-way categorization that reflects adherence or non-adherence to the age-specific recommendations for each dose.[9] Doses administered were defined as "on-time," "delayed, as a first instance" of delayed vaccination in the schedule, or "delayed, with prior instances" of delay at prior vaccination encounters. Any dose that was recorded as having been administered ≥4 after the recommended age was considered delayed. Age (in days) at vaccination was used as the cut off for on-time versus delayed vaccination, and history of delayed vaccination any prior dose was used to assign children to "delayed, with prior instances" (Table 2.2).

Age in days at vaccination was calculated by subtracting the child's birthdate from the vaccination date recorded on a child's immunization card. Where month or year of birth were missing, other available dates in the survey were cross-referenced to define plausibility bounds. For cases in which the day of birth was missing but the date of BCG vaccination complete (*n*=14,243), age at vaccination was imputed drawing from the distribution of known values for age at BCG vaccination and then birthdate was back-calculated by subtracting the imputed age in days from the date at BCG vaccination.

Known predictors of vaccination timeliness and completion were also explored and used as covariates in analysis. Birth setting was defined as: institutional delivery in public sector setting. institutional delivery in private sector setting, non-institutional delivery with presence of skilled healthcare attendant, non-institutional delivery with traditional birth attendant, or non-institutional delivery with no assistance. Child's rank in the birth order, adjusting for multiple

births, was also considered. Missed opportunity for co-administration was assessed using a dichotomous variable for each of the 3 instances where Penta and polio co-administration should occur. Maternal educational attainment, parental marital status, household wealth, and residence location were assessed using the categorical definitions defined by DHS.[26]

Statistical Analysis

Delayed vaccination across levels of child characteristics was assessed and significance of differences evaluated. Using multinomial logistic regression, predictors were evaluated for categories of dose-specific delayed vaccination: (1) delayed, first instance versus on-time and (2) delayed, prior instance versus on-time. Then, the primary association of interest was explored, separately evaluating the association between delayed receipt of BCG, Penta1, Penta2, Penta3, and measles and schedule completion in a set of logistic regression models that included children conditional on having received the vaccine. ORs, average marginal effects and predicted probabilities of the outcome were estimated for first instance of delayed vaccination and repeated delays in vaccination. Average marginal effects and predicted probabilities of the outcome allow for making more appropriate comparisons across models due to failing to assume that unobserved heterogeneity is the same across model samples conditional on having received a vaccine, such as children who receive BCG differ from children who receive doses later in the schedule. Covariates that were identified as significantly associated with vaccination delays were retained for controls in the adjusted models exploring associations between dose-specific delays and schedule completion. Necessitating a control for time and place in the multi-country models, indicator dummy variables for each country and continuous variables for year and child's age at interview were used. As a sensitivity analysis, country-stratified models were used to evaluate

the heterogeneity in effects across countries in the sample. All analyses used country-specific sampling weights and survey design strata variables to account for the complex sample design. Unweighted case frequencies and weighted proportions are reported. All analyses were conducted in Stata, version 16.1.

Results

A total of 136,745 children aged 12–35 months were surveyed in the most recent DHS waves during 2010–2019 across the 33 included countries. After selecting the youngest child from households with multiple age-eligible children, the availability of vaccination records in 132,405 children was assessed. Across country surveys, the median proportion of age-eligible children who had a vaccination card available during the interview was 58% (IQR=46%–63%). In total, 61,399 age-eligible children were excluded (Table 2.3), owing either to having no vaccination card available (*n*=53,659) or implausible/missing vaccination dates sporadically throughout their records (*n*=8,740). Although characteristics of children stratified on the restriction criteria did not differ substantially between groups, the analytic sample (*n*=70,006) represented children who had considerably higher rates of vaccination schedule completion overall at the time of interview than children excluded from analysis (Table 2.3).

In terms of under-vaccination in the sample, the proportion of children missing recommended doses or receiving delayed doses increased with each subsequent visit across the vaccination milestone visits, using BCG, penta1–3, and measles vaccination status as representative of the 5 vaccine administration encounters across the schedule as penta1–3 are administered concomitantly with polio1–3 (Figure 2-1). Though <1% of children received no vaccines in their first year of life, the other 20% of children who did not complete their schedule by age 12 months had missed an important number of doses when considering the full 8-dose

recommended series: 5% missing 4–7 doses, 6% missing 2–3 doses, and 9% missing ≥1 dose (country-specific estimates are in Table 2.1).

Among vaccinated children across countries, late administration by ≥4 weeks was: 25.9% for BCG; 23.5% for the first, 38.2% for the second, and 49.1% for the third doses of Penta; and 63.6% for measles (Table 2.4). The proportion of children receiving delayed vaccination repeatedly across the schedule was consistently highest for higher birth order (7+) children or those who were born in non-institutional settings with no skilled assistance. By contrast, the proportion of delayed vaccination trended substantially lower for children born to mothers with higher levels of educational attainment and household wealth. For example, in the wealthiest households, only 35.3% of children were delayed for Penta3 vaccination compared with 58.7% in the poorest households. Similarly, there was more than a significant difference in the prevalence of delayed Penta3 vaccination between children of mothers who had high educational attainment (24.4%) versus no education (60.8%). For children who were vaccinated against measles, the proportion affected by delays did not vary as substantially across childhood and maternal predictors as was observed for other vaccination delays. Nonetheless, except for parental marital status and child sex, all sociodemographic characteristics demonstrated some level of significant association with delayed vaccination, either as a first instance or following prior delays ($p<0.05$) (Table 2.6).

Children with delayed vaccination were at increased odds of not finishing their schedules by age 12 months compared with children who received on-time vaccination (Table 2.5). The magnitude of this association was large for children who received delayed vaccination against measles as the first occurrence of delay in the schedule (AOR=3.76, 95% CI=3.37, 4.15) or

following a pattern of delayed vaccination across the schedule (AOR=8.21, 95% CI=7.50, 8.91) compared with on-time vaccination in children. However, children who were both delayed in receiving measles and did not complete their schedules by age 12 months often did finish their schedules at an older age. The median age of measles vaccination for these children was 4.25 months after the recommended age (13.25 months), resulting in their under-vaccination status at age 12 months.

Patterns of repeated delays across the childhood schedule resulted in a significantly higher probability ($p<0.001$) of drop-off from the recommended series compared with children who were receiving on-time vaccination (Penta1 delay with prior delays: 21.2% higher; measles delay with prior delays: 21.5% higher) (Table 2.5). Both "first instance" delays and "with prior" delays at the first dose of Penta significantly predicted incompletion rates, which were sustained for delays at Penta2, Penta3, and measles, though with predictions of the probability of incompletion declining with each subsequent dose (Figure 2-2). In the country-stratified models explored as a sensitivity analysis, there was variation across countries in the magnitude of association between dose-specific delays and not finishing the basic childhood vaccination schedule (Supplemental Figures 2-1, 2-2, and 2-3). However, children with vaccination delays in ≥1 dose compared with on-time doses consistently showed a higher probability of not completing the schedule.

Discussion

Assessment of vaccination timeliness is essential to identifying age-specific risks of VPDs, which continue to contribute to under-5 mortality in SSA.[27,28] Similarly, defining the role that delayed vaccination plays in hindering the completion of the recommended schedule in the

first year of life is needed for evidencing the value of programmatic interventions that target timely vaccination as a means to improving protective coverage overall. Although uptake of individual vaccine doses has improved (i.e., Penta3 increased from 77% to 81% in Eastern and Southern Africa and 65% to 70% in West and Central Africa during 2010–2019), aggregate measures of coverage are an imprecise predictor of the population risk profile for VPDs. These measures do not account for the timing of vaccination and the resulting age-specific protection, or lack thereof when delays lead to additional delays, or eventual dropout and under-vaccination.[29] This study explored the association between children having dose-specific delays and completing their immunization schedules before age 12 months. Using recent nationally representative survey data from 33 SSA nations, the findings suggest that dose-specific delays are common and that those delays lead to a significantly higher probability of dropping off the schedule, resulting in prolonged susceptibility to specific VPDs beyond the first year of life.

To the authors' knowledge, previous studies on the determinants of under-vaccination in SSA have not considered the role of adherence to age-specific vaccination recommendations, besides on-time vaccination at birth. Studies in both low- and higher-income settings alike have found that the risk of programmatic dropout associated with delayed initiation of vaccination at birth is significant.[16,17,30] In this study, delayed administration of any dose was significantly associated with an increased likelihood of not completing the immunization schedule during the first year of life. Across immunization programs in SSA, education and outreach designed to improve community demand for on-time vaccination services could lessen the programmatic burden of follow-up when children fall behind in their schedules and reduce the resulting risk of under-vaccination. However, vaccine stock-outs and other service disruptions are often

unavoidable barriers to access. In these scenarios, outreach and catch-up campaigns remain important for bringing children up-to-date on their vaccination.

It is worth clarifying that some delays may result from intentional adjustments to the schedule for individual children following delayed initiation of a multi-dose series. This is because a 4-week interval is recommended between doses to avoid blunting the immune response.[8] Nonetheless, across countries, delays were predictive of subsequent delays that extended beyond the minimum recommended interval between doses, and even predictive of dropout, both of which can contribute to under-vaccination after the first year of life. For example, instead of using the minimum interval required, 88% and 86% of delayed Penta2 and Penta3 vaccination, respectively, occurred >4 weeks after delayed receipt of the previous dose in the series.

Consistent with immunization research in SSA,[14,15,31–33] delayed vaccination observed across countries was most prevalent among families with socioeconomic and educational disadvantages. Although, notably, the prevalence of delayed measles vaccination as a first instance of delay did not differ as substantially across wealth and maternal education as compared to the variation across socioeconomic group observed for delayed doses earlier in the schedule. Instead, there were consistently high levels of delay for receipt of measles (>60%). Since the launch of the Expanded Programme on Immunization in 1979, countries have measured the success of their immunization programs by the coverage achieved with Penta3. Using administrative coverage of Penta3, immunization program performance may appear to be improving, yet when delays result in under-vaccination against measles, which currently is not tracked at a global level, the threat of a measles resurgence becomes an important concern and one that has come to recent fruition in a number of SSA countries.[34]

Considering existing challenges to reducing under-vaccination in the context of the destabilizing threat that pandemic spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) poses for weak public health systems, immunization programs must consider how to prioritize timely vaccination throughout the course of the schedule to ensure age-specific protection and to increase the likelihood of completing all recommended vaccines. Although standard outreach activities may not be feasible, continued emphasis on education for mothers and providers about the contingency plans for completing their infants' immunization schedules, either through campaigns or health facility visits, will be needed. Where substantial concern for interrupted immunization activity may exist,[35] immunization programs could also consider vaccinating against measles at younger infant ages in settings that warrant such an approach.[8]

Limitations

Despite contributing a new perspective on vaccination timeliness and under-vaccination in SSA, the approach and data sources used to study this association have some limitations. Children were excluded if they lacked complete vaccination histories, including those who had died prior to the interview. Both subpopulations likely differ substantially in their overall health, risk factors, and access to immunization from surviving children with complete records, which limits the generalizability of this study. Assuming that delayed vaccination is correlated with access to services and availability of a vaccination card is an indicator of access, it might also be assumed that delayed vaccination and dropout may even more frequently occur in children who do not have records. This would lead to underestimating the prevalence of vaccination delays and their contribution to overall completion rates. On the other hand, in the absence of electronic immunization registries, this study may have incorrectly classified vaccination outcomes if dates

were not correct or administered doses were not documented. Though, data quality measures are embedded in the DHS program to change implausible dates to missing and survey data are generally considered the gold standard for assessing immunization uptake.[36,37] Although the surveys are cross-sectional, the availability of vaccination dates for the sample allowed the authors to establish the sequential timing of vaccine administration across the schedule and temporally associate delays, classified as a first-time delay or prior delays, with vaccination schedule completion as the ultimate outcome in the timing sequence. Finally, programming constraints and barriers to access predictive of under-vaccination undoubtedly vary across countries in SSA. Though the heterogeneity in the magnitude and direction of the main effects across countries was explored, identifying and adjusting for country-specific observed and unobserved confounding was outside the scope of this research aim to generally establish delays as predictive of overall vaccination status in SSA. Future studies on the country-specific nuances of each program could contribute more precise recommendations on how to intervene in cases where clear patterns of bottlenecks in schedule completion arise due to dose-specific delays.

Conclusions

This study identified delayed vaccination at birth and delays in subsequent doses as important impediments to completing the routine schedule in SSA. Although children in SSA who have contact with the immunization program likely have higher probability of survival associated with general health services access, the benefit of on-time and full immunization of individuals extends beyond the individuals themselves. Targeting on-time delivery of vaccines across the immunization schedule among individuals and communities may contribute to achieving greater levels of protection at the population level.

Table 2.1 Countries and sample sizes covered in Demographic Health Surveys (DHS) in the region of sub-Saharan Africa from 2010-2019

Country	Year	DHS Wave	Children 12-35m in sample	Observations used in analysis	% under-vaccinated by 12 months (study outcome)	% under-vaccinated by 12 months, by number of doses missing			
						1	2	3-7	8 (all)
Angola	2015-16	7	5524	1798	46%	12%	3%	24%	7%
Burkina Faso	2010	6	5467	4076	16%	9%	1%	5%	0%
Benin	2017-18	7	4865	3066	32%	15%	1%	13%	4%
Burundi	2016-17	7	4980	3128	12%	9%	1%	2%	0%
Congo Dem. Republic	2013-14	6	6858	729	23%	12%	1%	9%	2%
Congo	2011-12	6	3569	1300	36%	11%	5%	20%	0%
Cote D'Ivoire	2011-12	6	2841	1547	45%	21%	2%	18%	4%
Cameroon	2011	6	4361	1995	28%	14%	2%	10%	2%
Ethiopia	2016	7	3855	1647	43%	20%	4%	15%	3%
Gabon	2012	6	2344	1250	73%	11%	8%	54%	1%
Ghana	2014	6	2262	1770	19%	13%	2%	4%	0%
Gambia	2013	6	3133	2474	24%	16%	3%	5%	0%
Guinea	2018	7	2677	1307	70%	23%	2%	28%	17%
Kenya	2014	6	8068	5068	23%	16%	2%	4%	0%
Comoros	2012	6	1210	640	33%	16%	3%	13%	1%
Liberia	2013	6	2709	1107	33%	16%	2%	15%	1%
Lesotho	2014	6	1228	857	26%	16%	4%	5%	0%
Mali	2018	7	3675	1396	38%	21%	3%	12%	1%
Malawi	2015-16	7	6500	4053	22%	16%	2%	3%	1%
Mozambique	2011	6	4233	2894	36%	17%	4%	13%	2%
Nigeria	2018	7	11893	3515	42%	19%	3%	18%	3%
Niger	2012	6	4525	2178	38%	21%	3%	13%	2%
Namibia	2013	6	1973	1077	18%	11%	2%	5%	0%

Rwanda	2014-15	6	3070	2437	30%	29%	0%	1%	0%
Sierra Leon	2013	6	4096	2573	33%	18%	1%	12%	1%
Senegal	2017	7	4616	2833	22%	14%	2%	5%	1%
Chad	2014-15	6	6200	897	57%	13%	4%	30%	9%
Togo	2013-14	6	2678	1579	29%	19%	1%	9%	0%
Tanzania	2015-16	7	4034	2731	24%	15%	2%	6%	1%
Uganda	2016	7	5838	3392	36%	20%	5%	11%	1%
South Africa	2016	7	1346	632	22%	15%	4%	4%	0%
Zambia	2018-19	7	3811	2397	20%	14%	2%	3%	0%
Zimbabwe	2015	7	2307	1663	21%	14%	3%	4%	0%
Median			**3855**	**1798**	**30%**	**16%**	**2%**	**10%**	**1%**
First Quartile			1210	1300	22%	13%	2%	5%	0%
Third Quartile			4980	2833	38%	19%	3%	15%	2%
Total (% mean)			**136746**	**70006**	**31%**	**16%**	**2%**	**11%**	**2%**

Table 2.2 Age-specific recommendations for the basic immunization schedule endorsed by WHO

Age at administration	Vaccines	Minimum acceptable age (days)	Delays initiated (age in days)
Birth	BCG, OPV0	0 days	Greater or equal to 28 days
6 [8] weeks	Penta1, OPV1	42 [56] days	Greater than 70 [84] days
10 [12/16] weeks	Penta2, OPV2	Age in days at previous dose + 28	Greater than 98 [112/140] days
14 [16/24] weeks	Penta3, OPV3	Age in days at previous dose + 28	Greater than 126 [140/196] days
9 months	Measles	252 days	Greater than 280 days

*Four countries in the sample use the schedules denoted in brackets

Table 2.3 Characteristics of children 12-35 months according to data availability for assessing vaccination status. Only children with complete dates included in analytic sample

	Card verification (n=78,746)		Maternal recall (n=53,659)	Overall (n=132,405)
	Complete dates	Incomplete dates		
Child's age	**70,006**	**8,740**	**53,659**	**132,405**
12-23 months	50%	50%	50%	50%
24-35 months	50%	50%	50%	50%
Child's sex	**70,006**	**8,740**	**53,659**	**132,405**
Male	57%	55%	45%	52%
Female	43%	45%	55%	48%
Birth order	**70,006**	**8,740**	**53,659**	**132,405**
1st	23%	22%	22%	23%
75% 2nd to 3rd	37%	36%	34%	36%
4th to 5th	29%	29%	30%	29%
6th +	11%	13%	14%	12%
Birth setting	**69,180**	**8,616**	**53,049**	**130,845**
Institutional, public	66%	61%	50%	59%
Institutional, private	9%	8%	8%	9%
Home, skilled attendant	2%	3%	3%	2%
Home, traditional attendant	21%	25%	34%	26%
Home, no attendant	3%	3%	5%	4%
Vaccination status, according to card or recall	**70,006**	**8,740**	**53,659**	**132,405**
Fully vaccinated	21%	26%	78%	43%
Not fully vaccinated	79%	74%	22%	57%
Maternal age (at child's birth)	**70,006**	**8,740**	**53,659**	**132,405**
Under 19	15%	17%	18%	16%
20-29	52%	52%	52%	52%
30-39	29%	28%	26%	28%
40-49	4%	4%	4%	4%
Maternal education	**69,995**	**8,739**	**53,655**	**132,389**
None	36%	37%	44%	39%
Primary	34%	35%	29%	32%
Secondary	27%	25%	24%	25%
Higher	3%	3%	3%	3%
Household wealth quint.	**70,006**	**8,389**	**53,659**	**132,405**
Poorest	20%	22%	25%	22%
Poorer	21%	22%	22%	22%
Middle	21%	21%	19%	20%
Richer	20%	19%	18%	19%

Richest	18%	16%	15%	17%
Place of residence	**70,006**	**8,389**	**53,659**	**132,405**
Urban	34%	34%	33%	34%
Rural	66%	66%	67%	66%

Table 2.4 Proportion of children 12-35 months with delayed vaccination across the immunization series stratified by descriptive characteristics

	BCG (Birth)		Penta, 1st dose (6 or 8 wk)		Pent, 2nd dose (10, 12 or 16 wk)		Pent, 3rd dose (14, 16 or 24 wk)		Measles, 1st dose (9 mo.)	
	%	*p*[e]	%	*p*[e]	%	*p*[e]	%	*p*[e]	%	*p*[e]
Overall [c]	25.9%		23.5%		38.2%		49.1%		63.6%	
Child's sex		*0.33*		*0.24*		*0.46*		*0.51*		*0.23*
Male	25.7%		24.9%		38.4%		49.3%		63.9%	
Female	26.1%		25.4%		38.0%		49.0%		63.3%	
Child's age (at interview)		*0.20*		*0.61*		*0.05*		*0.02*		*0.01*
12-23 months	25.7%		25.1%		37.8%		48.6%		62.8%	
24-35 months	26.2%		25.3%		38.8%		49.9%		64.6%	
Birth order		*<0.001*		*<0.001*		*<0.001*		*<0.001*		*<0.001*
1st	21.8%		20.9%		32.8%		42.9%		59.3%	
2nd to 3rd	23.2%		22.7%		35.3%		46.4%		63.5%	
4th to 5th	29.0%		28.4%		42.2%		53.4%		66.2%	
6th +	35.9%		34.1%		49.5%		61.4%		66.9%	
Birth setting		*<0.001*		*<0.001*		*<0.001*		*<0.001*		*<0.001*
Institutional delivery, public	19.8%		0.2109		33.9%		45.3%		62.2%	
Institutional delivery, private	18.9%		0.1782		29.3%		39.0%		64.2%	
Home delivery, skilled attend.	35.7%		0.3164		45.7%		54.9%		62.2%	
Home delivery, trad.l attend.	45.7%		0.3942		54.1%		65.2%		67.7%	
Home delivery, no attend.	48.9%		0.3948		54.4%		64.7%		70.2%	
Fully immunized		*<0.001*		*<0.001*		*<0.001*		*<0.001*		*<0.001*
Incomplete	36.0%		40.6%		55.6%		60.9%		71.2%	
Complete	23.5%		21.6%		38.4%		47.5%		63.0%	
Not coadministered with Polio1	-		41.1%	*<0.001*	52.2%	*<0.001*	58.1%	*<0.001*	66.9%	*<0.001*
Not coadministered with Polio2	-		-		48.6%	*<0.001*	53.3%	*<0.001*	64.8%	*<0.001*

Not coadministered with Polio3	-		-		-		53.3%	*<0.001*	66.0%	*<0.001*
Mother's age (at childbirth)		*<0.001*		*<0.001*	1	*<0.001*		*<0.001*		*<0.001*
Under 20	28.0%		26.3%		40.3%		51.1%		61.7%	
20-29	25.2%		24.6%		36.9%		47.9%		63.3%	
30-39	25.6%		25.1%		38.8%		49.6%		64.7%	
40-44	29.1%		28.4%		43.1%		54.0%		66.8%	
Mother's educational attainment		*<0.001*		*<0.001*		*<0.001*		*<0.001*		*<0.001*
None	33.3%		33.3%		48.8%		60.8%		64.1%	
Primary	26.6%		23.9%		37.1%		48.4%		65.7%	
Secondary	17.4%		17.8%		28.7%		38.8%		61.3%	
Higher	10.1%		11.4%		17.9%		24.4%		57.6%	
Mother's marital status		*<0.001*		*<0.001*		*<0.001*		*<0.001*		*<0.001*
Never married	18.2%		19.6%		30.8%		38.3%		58.0%	
Formerly married	25.1%		25.3%		39.8%		50.5%		65.6%	
Currently married	26.6%		25.6%		38.7%		50.0%		64.0%	
Household wealth quintile		*<0.001*		*<0.001*		*<0.001*		*<0.001*		*<0.001*
Poorest	34.3%		31.9%		46.8%		58.7%		66.9%	
Poorer	31.5%		29.2%		43.3%		54.4%		64.9%	
Middle	27.1%		25.5%		39.2%		50.7%		63.5%	
Richer	21.3%		21.8%		34.9%		45.8%		62.4%	
Richest	14.1%		16.6%		25.8%		35.3%		60.2%	
Place of residence		*<0.001*		*<0.001*		*<0.001*		*<0.001*		*<0.001*
Rural	31.0%		28.0%		42.1%		53.6%		64.7%	
Urban	16.3%		19.7%		30.9%		40.7%		61.5%	
Observations [d]	**67,335**		**66,849**		**65,036**		**62,271**		**57,501**	

[a] All proportions in the pooled sample account for each country's survey design using sampling weights provided by DHS.
[b] Number of children age-eligible for inclusion who had a vaccination card available at the time of interview with complete dates for administered doses of BCG, Penta3, Polio3 and Measles if received.
[c] 'Overall' reflects the proportion of children vaccinated late, according to cutoffs defined in Table 1, regardless of being the first instance of delay or having a prior history of delayed vaccination, among children who were vaccinated.

[d] Differences in the number of observations between vaccination doses reflect dropout due to not receiving a dose or listwise deletion due to missing values for covariates/predictors. For BCG, 1,863 children did not receive the dose and another 808 children were excluded due to missing values for birth setting and/or maternal education; For Pentavalent, 1,982 (dose 1), 3,900 (dose 2) and 6,977 (dose 3) children did not receive doses in the vaccination series, and another 811, 796 and 758 children were excluded from the respective analytic samples due to incomplete vaccination dates, or missing values for birth setting or maternal education. For measles, 10,593 children did not receive the vaccine and another 729 children were excluded due to missing values for birth setting and/or maternal education.

[e] *p*-values are calculated from chi-square test for independence between levels of categorical characteristics

Table 2.5 Association between dose-specific delayed vaccination and not completing the basic immunization schedule by 12 months of age in children 12-35 months across 33 countries in sub-Saharan Africa. Logistic regression a results presented as OR[a] and AME[b]

	BCG [d]	Penta1	Penta2	Penta3	Measles	BCG [d]	Penta1	Penta2	Penta3	Measles
	Odds Ratio (OR) (95%CI)					Average Marginal Effect (AME) (95%CI)				
Delayed, first instance (ref = on-time)	1.93*** (1.83-2.02)	1.99*** (1.83-2.14)	1.88*** (1.74-2.02)	1.50*** (1.36-1.63)	3.76*** (3.37-4.15)	0.129*** (0.11-0.15)	0.131*** (0.11-0.15)	0.106*** (0.08-0.12)	0.056*** (0.04-0.07	0.106*** (0.09-0.12)
Delayed, prior instance (ref = on-time)	-	2.91*** (2.71-3.12)	2.79*** (2.63-2.94)	2.46*** (2.32-2.60)	8.21*** (7.50-8.91)		0.212*** (0.19-0.23)	0.186*** (0.17-0.21)	0.143*** (0.12-0.16)	0.215*** (0.20-0.23)
Observations	67,335	66,849	65,036	62,271	58,684	67,408	66,849	65,036	62,271	57,501

*** p<0.001

[a] For consistency across models for BCG, Penta1, Penta2, Penta3 and Measles, all models adjust for: continuous child age, birth order and setting; mother's age at childbirth and educational attainment by time of interview; and household wealth quintile and location (rural/urban); survey year and country. Models for Penta and Measles include controls for missed opportunities of vaccination associated with recommended concomitant vaccination of Penta and Polio at 6, 10 and 14 weeks. Not shown.

[b] Odds of not completing the basic immunization schedule by 12 months of age (i.e. receiving BCG, Penta1-3, Polio1-3 and Measles1) are compared between children who receive delayed vaccination and children who are vaccinated on-time. The three-level delay category captures two types of delay: first instance of delayed receipt in the schedule and delayed at a given instance after having experienced delays at prior vaccination instances.

[c] AME shows the average change in probability of the outcome when making a discrete level change in the categorical predictor defining delayed vaccination versus on-time vaccination, i.e. how much higher (or lower) the expected mean probability of not completing the vaccination series is in the study population when a child is delayed (either first instance or with prior delays) in receiving a specific vaccine dose versus receiving the dose on time, holding all other variables at their observed values.

[d] The only type of delay recognized for BCG is first instance because it is the first dose (administered at birth) in the series.

Table 2.6 Multinomial logistic regression results of factors associated with first instance/prior delays compared to on-time vaccination by vaccine. Results reported as adjusted Odds Ratios (aOR) and robust standard errors in parentheses

	BCG	Penta1		Penta 2		Penta3		Measles	
	Compared to on-time receipt								
Type of delay:	**First delay**	**First delay**	**Prior delays**	**First delay**	**Prior delays**	**First delay**	**Prior delays**	**First delay**	**Prior delays**
Child's sex (ref=male)									
Female	1.01	1.01	1.02	0.90*	1	1.01	0.96	1	0.96
	(0.02)	(0.04)	(0.03)	(0.03)	(0.03)	(0.04)	(0.02)	(0.03)	(0.02)
Child's birth order (ref=1st)									
Second	1.05	1.05	1.12*	1.22***	1.06	1.08	1.14**	1.17***	1.29***
	(0.04)	(0.06)	(0.06)	(0.07)	(0.04)	(0.06)	(0.04)	(0.05)	(0.05)
Third	1.20***	1.26***	1.34***	1.22**	1.29***	1.17*	1.29***	1.25***	1.51***
	(0.06)	(0.09)	(0.08)	(0.08)	(0.06)	(0.08)	(0.06)	(0.07)	(0.07)
Fourth or higher order	1.39***	1.48***	1.62***	1.28**	1.62***	1.27**	1.63***	1.12	1.64***
	(0.09)	(0.14)	(0.12)	(0.12)	(0.10)	(0.12)	(0.10)	(0.09)	(0.11)
Birth setting (ref=Institutional, public)									
Institutional, private	1.12*	0.98	1.05	1.02	1.02	0.94	1	1.03	1
	(0.06)	(0.08)	(0.08)	(0.07)	(0.06)	(0.07)	(0.05)	(0.05)	(0.05)
Non-institutional, skilled attendant	1.73***	0.99	1.42***	0.94	1.36**	0.9	1.18	0.88	1.18
	(0.15)	(0.13)	(0.14)	(0.12)	(0.14)	(0.14)	(0.13)	(0.12)	(0.12)
Non-institutional, traditional attendant	2.12***	1.07	1.98***	1.05	1.67***	1.02	1.60***	0.72***	1.33***
	(0.07)	(0.05)	(0.07)	(0.05)	(0.06)	(0.05)	(0.06)	(0.03)	(0.05)
Non-institutional, no attendant	2.14***	1.01	2.04***	1.08	1.78***	0.96	1.66***	0.83	1.49***
	(0.15)	(0.11)	(0.15)	(0.12)	(0.10)	(0.13)	(0.12)	(0.08)	(0.11)
Mother's age at childbirth (ref=15-19)									
20-29	0.86***	0.97	0.83***	0.79***	0.88***	0.93	0.85***	1.01	0.88**
	(0.04)	(0.06)	(0.04)	(0.05)	(0.04)	(0.06)	(0.04)	(0.05)	(0.04)
30-29	0.76***	0.81**	0.72***	0.87	0.75***	0.88	0.76***	1.04	0.80***
	(0.04)	(0.07)	(0.05)	(0.06)	(0.04)	(0.07)	(0.04)	(0.07)	(0.05)

44-44	0.76***	0.83	0.66***	0.86	0.71***	0.86	0.70***	1.1	0.82*
	(0.06)	(0.10)	(0.06)	(0.10)	(0.06)	(0.10)	(0.06)	(0.11)	(0.07)
Mother's educational attainment (ref=none)									
Primary	0.92**	0.85***	0.84***	0.86**	0.82**	0.90*	0.81***	1.13**	0.97
	(0.03)	(0.04)	(0.03)	(0.04)	(0.03)	(0.05)	(0.03)	(0.05)	(0.03)
Secondary	0.79***	0.68***	0.67***	0.65***	0.64***	0.78***	0.61***	1.27***	0.87**
	(0.03)	(0.05)	(0.04)	(0.04)	(0.03)	(0.05)	(0.03)	(0.06)	(0.04)
Higher	0.56***	0.58***	0.48***	0.47***	0.47***	0.61**	0.40***	1.24*	0.74***
	(0.07)	(0.09)	(0.09)	(0.08)	(0.05)	(0.09)	(0.04)	(0.11)	(0.07)
Mother's marital status (ref=never married)									
Married, currently	1.00	0.95	0.99	1	0.98	1.28**	1.07	0.96	1.01
	(0.06)	(0.08)	(0.08)	(0.08)	(0.06)	(0.11)	(0.06)	(0.06)	(0.06)
Married, formerly	1.01	1.1	1	1.13	1.09	1.23	1.19*	0.91	1.09
	(0.08)	(0.12)	(0.10)	(0.12)	(0.09)	(0.13)	(0.09)	(0.08)	(0.09)
Household wealth quintile (ref=poorest)									
Poorer wealth quintile	0.91**	0.87**	0.88**	0.94	0.85***	0.9	0.83***	0.98	0.91*
	(0.03)	(0.05)	(0.04)	(0.05)	(0.03)	(0.05)	(0.03)	(0.04)	(0.03)
Middle wealth quintile	0.80***	0.80***	0.78***	0.91	0.76***	0.91	0.76***	1.02	0.87***
	(0.03)	(0.05)	(0.04)	(0.05)	(0.03)	(0.05)	(0.03)	(0.05)	(0.03)
Richer wealth quintile	0.69***	0.78***	0.69***	0.92	0.69***	0.88*	0.70***	1.04	0.84***
	(0.03)	(0.05)	(0.04)	(0.06)	(0.03)	(0.05)	(0.03)	(0.05)	(0.04)
Richest wealth quintile	0.51***	0.80**	0.54***	0.74***	0.56***	0.74***	0.55***	1.16*	0.72***
	(0.03)	(0.07)	(0.04)	(0.06)	(0.03)	(0.06)	(0.03)	(0.07)	(0.04)
Residence location (ref=urban)									
Rural	1.45***	1.15**	1.33***	1.06	1.35***	1.05	1.32***	0.86**	1.18***
	(0.06)	(0.06)	(0.07)	(0.06)	(0.06)	(0.06)	(0.05)	(0.04)	(0.05)
Year of interview	0.90*	0.84*	0.88	1.08	0.89*	0.94	0.96	0.98	0.92
	(0.05)	(0.06)	(0.06)	(0.07)	(0.05)	(0.06)	(0.05)	(0.05)	(0.05)
Child's age in months	1.01***	1	1.01***	1.01**	1.01***	1	1.01***	1	1.01***
	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)	(0.00)

Missed opportunity for vaccination (ref=Polio and Penta co-administered)									
At 6 weeks	-	0.36***	0.55***	1.27*	0.60***	1.38**	0.74***	1.28***	0.97
		(0.02)	(0.03)	(0.12)	(0.04)	(0.13)	(0.05)	(0.10)	(0.06)
At 10 weeks	-			0.54***	0.73***	1	0.84**	1.30***	0.91
				(0.05)	(0.05)	(0.10)	(0.05)	(0.10)	(0.06)
At 14 weeks	-					0.73***	0.87**	1.25***	0.74***
						(0.06)	(0.05)	(0.09)	(0.04)
Observations	**67,335**	**66,849**		**65,036**		**62,271**		**58,684**	

* p<0.05 ** p<0.01 *** p<0.001

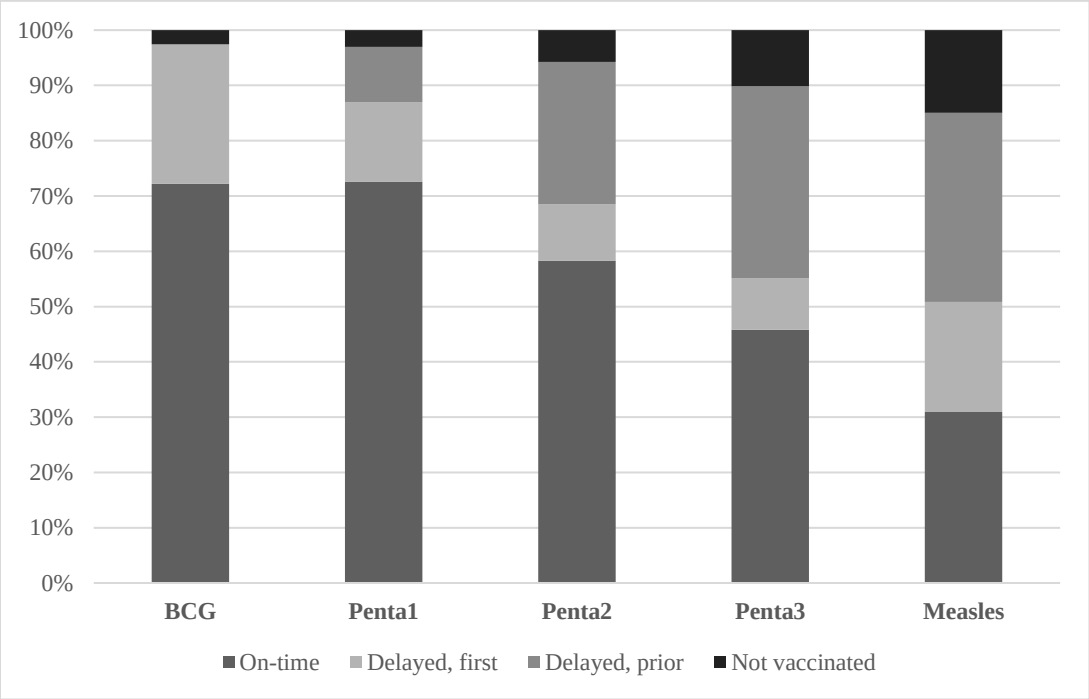

Figure 2-1 Percentage of children by vaccination status across the recommended series in the pooled analytic sample, weighted using country weights provided by DHS

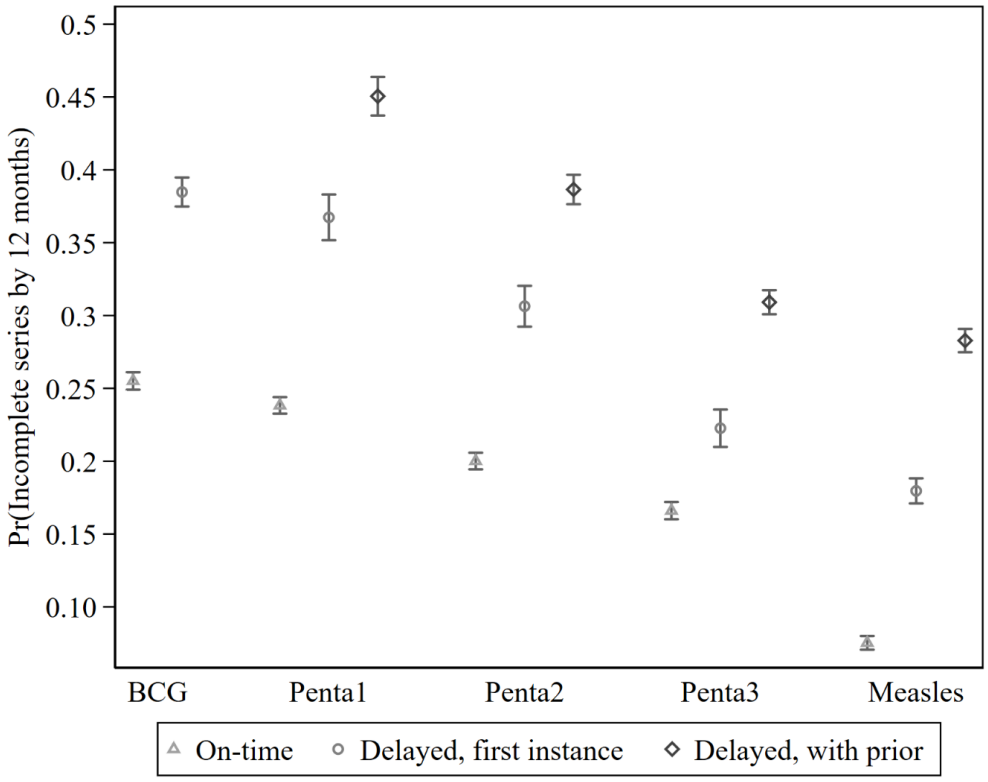

Figure 2-2 Predicted probability of not being fully vaccinated by 12 months of age for categories of vaccination timeliness at each dose: on-time, delayed (first instance) or delayed (with prior instances)

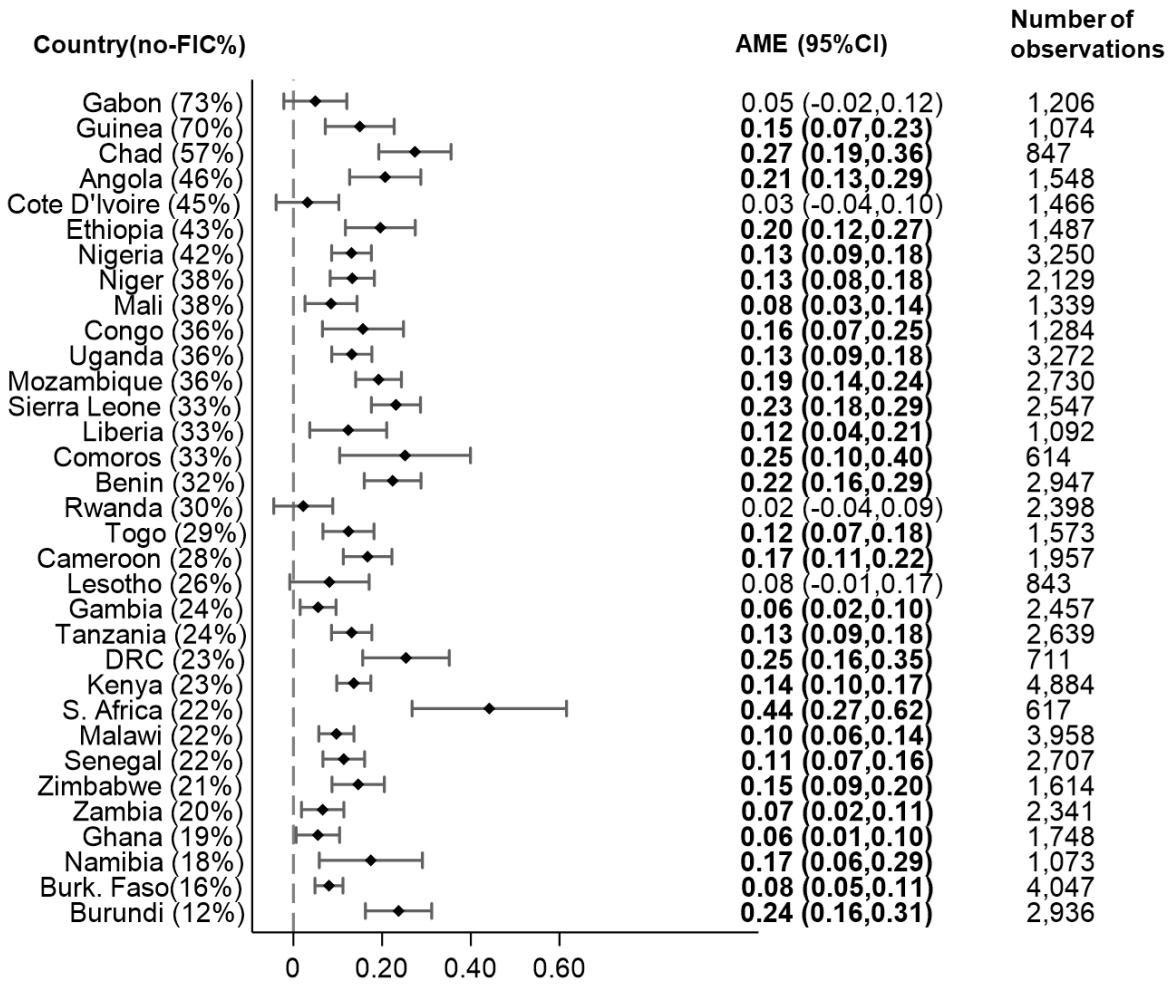

Figure 2-3 Country-stratified associations between dose-specific delayed vaccination (first instance delay vs. on-time administration of BCG) and not completing the basic immunization schedule by 12 months of age in children 12-35 months in 33 sub-Saharan African

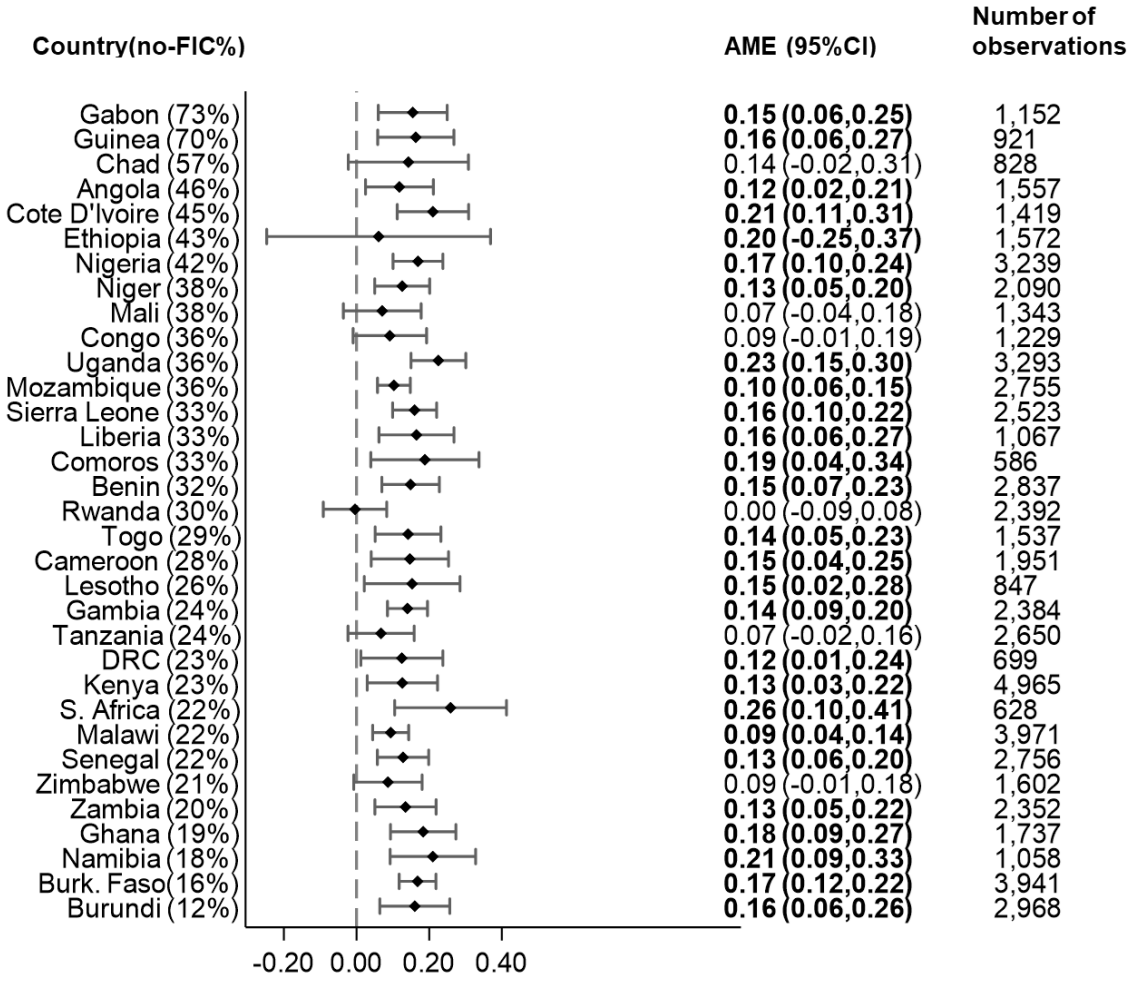

Figure 2-4 Country-stratified associations between dose-specific delayed vaccination (first instance delay vs. on-time administration of Penta1) and not completing the basic immunization schedule by 12 months of age in children 12-35 months in 33 SSA

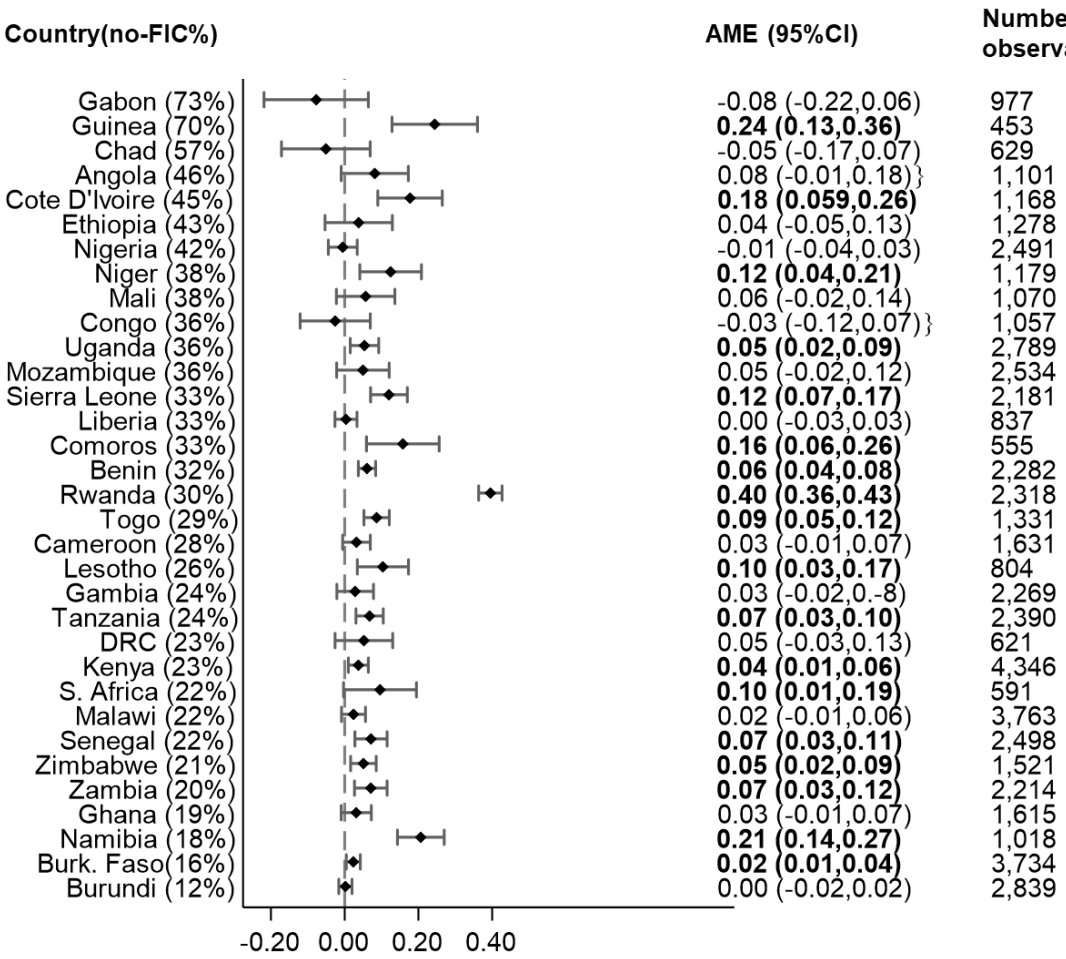

Figure 2-5 Country-stratified associations between dose-specific delayed vaccination (first instance delay vs. on-time administration of measles) and not completing the basic immunization schedule by 12 months of age in children 12-35 months in 33 SSA

References

1. You D, Hug L, Ejdemyr S, et al. Global, regional, and national levels and trends in under-5 mortality between 1990 and 2015, with scenario-based projections to 2030: a systematic analysis by the UN Inter-Agency Group for Child Mortality Estimation. *Lancet*. 2015;386(10010):2275–2286. https://doi.org/10.1016/s0140-6736(15)00120-8.
2. Victora CG, Harris Requejo J, Barros AJD, et al. Countdown to 2015: a decade of tracking progress for maternal, newborn, and child survival. *Lancet*. 2016;387(10032):2049–2059. https://doi.org/10.1016/s0140-6736(15)00519-x.
3. Chang AY, Riumallo-Herl C, Perales NA, et al. The equity impact vaccines may have on averting deaths and medical impoverishment in developing countries. *Health Aff (Millwood)*. 2018;37(2):316–324. https://doi.org/10.1377/hlthaff.2017.0861.
4. Chopra M, Bhutta Z, Blanc DC, et al. Addressing the persistent inequities in immunization coverage. *Bull World Health Organ*. 2020;98(2):146–148. https://doi.org/10.2471/blt.19.241620.
5. ICF International. The DHS Program STATcompiler. MEASURE DHS. http://www.statcompiler.com. Published 2015. Accessed April 20, 2020.
6. Sartorius B, Cohen C, Chirwa T, Ntshoe G, Puren A, Hofman K. Identifying high-risk areas for sporadic measles outbreaks: lessons from South Africa. *Bull World Health Organ*. 2013;91(3):174–183. https://doi.org/10.2471/blt.12.110726.
7. Clark A, Sanderson C. Timing of children's vaccinations in 45 low-income and middle-income countries: an analysis of survey data. *Lancet*. 2009;373(9674):1543–1549. https://doi.org/10.1016/s0140-6736(09)60317-2.
8. Recommended Routine Immunizations for Children. WHO. http://www.who.int/immunization/documents/positionpapers/. Published 2019. Accessed October 2, 2020.
9. Immunisation Agenda 2030: A Global Strategy to Leave No One Behind. WHO. https://www.who.int/immunization/immunization_agenda_2030/en/. Published 2020. Accessed October 2, 2020.
10. Akmatov MK, Kimani-Murage E, Pessler F, et al. Evaluation of invalid vaccine doses in 31 countries of the WHO African Region. *Vaccine*. 2015;33(7):892–901. https://doi.org/10.1016/j.vaccine.2014.10.089.
11. Miyahara R, Jasseh M, Gomez P, et al. Barriers to timely administration of birth dose vaccines in The Gambia, West Africa. *Vaccine*. 2016;34(29):3335–3341. https://doi.org/10.1016/j.vaccine.2016.05.017.
12. Mbengue MAS, Mboup A, Ly ID, et al. Vaccination coverage and immunization timeliness among children aged 12-23 months in Senegal: a Kaplan-Meier and Cox regression analysis approach. *Pan Afr Med J*. 2017;27(suppl 3):8. https://doi.org/10.11604/pamj.supp.2017.27.3.11534.
13. Ashbaugh HR, Hoff NA, Doshi RH, et al. Predictors of measles vaccination coverage among children 6–59 months of age in the Democratic Republic of the Congo. *Vaccine*. 2018;36(4):587–593. https://doi.org/10.1016/j.vaccine.2017.11.049.
14. Masters NB, Wagner AL, Carlson BF, Boulton ML. Vaccination timeliness and co-administration among Kenyan children. *Vaccine*. 2018;36(11):1353–1360. https://doi.org/10.1016/j.vaccine.2018.02.001.

15. Boulton ML, Carlson BF, Wagner AL, Porth JM, Gebremeskel B, Abeje Y. Vaccination timeliness among newborns and infants in Ethiopia. *PLoS One*. 2019;14(2):1–13. https://doi.org/10.1371/journal.pone.0212408.
16. Kiely M, Boulianne N, Talbot D, et al. Impact of vaccine delays at the 2, 4, 6 and 12 month visits on incomplete vaccination status by 24 months of age in Quebec, Canada. *BMC Public Health*. 2018;18:1364. https://doi.org/10.1186/s12889-018-6235-6.
17. Yusuf H, Daniels D, Smith P, Coronado V, Rodewald L. Association between administration of the hepatitis B and 4:3:1:3 vaccine series. *JAMA*. 2000;284(8):978–983. https://doi.org/10.1001/jama.284.8.978.
18. Guerra FA. Delays in immunization have potentially serious health consequences. *Pediatr Drugs*. 2007;9(3):143–148. https://doi.org/10.2165/00148581-200709030-00002.
19. Zaman SMA, Howie SRC, Ochoge M, et al. Impact of routine vaccination against Haemophilus influenzae type b in The Gambia: 20 years after its introduction. *J Glob Health*. 2020;10(1):010416. https://doi.org/10.7189/jogh.10.010416.
20. Cutts FT, Izurieta HS, Rhoda DA. Measuring coverage in MNCH: design, implementation, and interpretation challenges associated with tracking vaccination coverage using household surveys. *PLoS Med*. 2013;10(5):e1001404. https://doi.org/10.1371/journal.pmed.1001404.
21. ICF International. The DHS Program: Who We Are. https://www.dhsprogram.com/Who-We-Are/About-Us.cfm. Published 2020. Accessed April 20, 2020.
22. Corsi DJ, Neuman M, Finlay JE, Subramanian S V. Demographic and health surveys: a profile. *Int J Epidemiol*. 2012;41(6):1602–1613. https://doi.org/10.1093/ije/dys184.
23. ICF International. Demographic and Health Survey Sampling and Household Listing Manual. Calverton, MD; 2012.
24. Croft TN, Marshall AMJ, Allen CK. Guide to DHS Statistics, DHS-7. Rockville, MD; 2018. https://www.dhsprogram.com/pubs/pdf/DHSG1/Guide_to_DHS_Statistics_DHS-7.pdf. Accessed October 8, 2020..
25. ICF International. Demographic and Health Surveys Methodology: Interviewer's Manual. Calverton, MD; 2012. https://www.dhsprogram.com/pubs/pdf/DHSM1/DHS6_Interviewer_Manual_19Oct2012_DHSM1.pdf. Accessed October 2, 2020.
26. ICF International. Standard Recode Manual for DHS 6. ICF International/MEASURE DHS; 2013.
27. McAllister DA, Liu L, Shi T, et al. Global, regional, and national estimates of pneumonia morbidity and mortality in children younger than 5 years between 2000 and 2015: a systematic analysis. *Lancet Glob Health*. 2019;7(1):e47–e57. https://doi.org/10.1016/s2214-109x(18)30408-x.
28. Troeger C, Blacker BF, Khalil IA, et al. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of diarrhoea in 195 countries: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Infect Dis*. 2018;18(11):1211–1228. https://doi.org/10.1016/s1473-3099(18)30362-1.
29. WHO. WHO Immunization, Vaccines and Biologicals Measles Surveillance Data. http://www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/active/measles_monthlydata/en/#. Published 2019. Accessed August 6, 2019.
30. Emmanuel OW, Samuel AA, Helen KL. Determinants of childhood vaccination completion at a peri-urban hospital in Kenya, December 2013–January 2014: a case

control study. *Pan Afr Med J*. 2015;20:277. https://doi.org/10.11604/pamj.2015.20.277.5664.
31. Odutola A, Afolabi MO, Ogundare EO, et al. Risk factors for delay in age-appropriate vaccinations among Gambian children. *BMC Health Serv Res*. 2015;15:346. https://doi.org/10.1186/s12913-015-1015-9.
32. Akmatov MK, Mikolajczyk RT. Timeliness of childhood vaccinations in 31 low and middle-income countries. *J Epidemiol Community Health*. 2012;66(7):e14. https://doi.org/10.1136/jech.2010.124651.
33. Bangura JB, Xiao S, Qiu D, Ouyang F, Chen L. Barriers to childhood immunization in sub-Saharan Africa: a systematic review. *BMC Public Health*. 2020;20:1108. https://doi.org/10.1186/s12889-020-09169-4.
34. Scobie HM, Ilunga BK, Mulumba A, et al. Antecedent causes of a measles resurgence in the Democratic Republic of the Congo. *Pan Afr Med J*. 2015;21:30. https://doi.org/10.11604/pamj.2015.21.30.6335.
35. Nelson R. COVID-19 disrupts vaccine delivery. *Lancet Infect Dis*. 2020;20(5):546. https://doi.org/10.1016/s1473-3099(20)30304-2.
36. Danovaro-Holliday MC, Dansereau E, Rhoda DA, Brown DW, Cutts FT, Gacic-Dobo M. Collecting and using reliable vaccination coverage survey estimates: summary and recommendations from the "Meeting to share lessons learnt from the roll-out of the updated WHO Vaccination Coverage Cluster Survey Reference Manual and to set an operational. *Vaccine*. 2018;36(34):5150–5159. https://doi.org/10.1016/j.vaccine.2018.07.019.
37. Cutts FT, Claquin P, Danovaro-Holliday MC, Rhoda DA. Monitoring vaccination coverage: defining the role of surveys. *Vaccine*. 2016;34(35):4103–4109. https://doi.org/10.1016/j.vaccine.2016.06.053.

Chapter 3 Vaccination Outcomes Among Children With a Decedent Sibling Under-Five Years: An Analysis of the Demographic Health Survey from 33 African Nations

Abstract

Introduction: Low vaccination coverage in areas with unacceptably high rates of under-five death pose serious challenges for improving child health. Characterizing vaccination patterns in populations affected by the experience of premature under-five death may yield important lessons for immunization programs. This study explores the potential association between the community and family experience with a child under-five prematurely dying and vaccination outcomes in surviving children in sub-Saharan Africa (SSA).

Methods: Using childhood vaccination records and women's birth histories collected by Demographic and Health Surveys (DHS) in 33 SSA countries during 2010-2019, children 12-23 months who had one or more siblings born in the preceding 10-years prior to the survey were identified. Vaccination outcomes for children were compared between those who had at least one decedent older sibling and those who only had surviving siblings. Associations using binomial models with a logit link and adjustment for clustering in the survey design at the primary sampling unit were estimated. Modification of family experience with under-five death by under-five mortality (U5M) strata at sub-national levels was also explored.

Results: 52,687 children with vaccination records who had older siblings were identified across 33 Demographic and Health Surveys conducted between April, 2010, and January, 2019. On average, children evaluated for vaccination outcomes had 2.3 older siblings born within the prior 10 years and 20% had at least one decedent sibling. Having a decedent sibling was associated

with significantly lower odds of children being fully vaccinated at the time of interview, adjusting for geo-social factors (adjusted Odds Ratio [aOR] 0.88, 95%CI: 0.78-0.97). This association was slightly attenuated after controlling for mother characteristics (aOR: 0.89; 95%CI: 0.84-0.95). No effect modification due to variation in sub-national U5M was observed (*p* for interaction = 0.44); however, residing in a higher U5M strata was independently associated with significantly lower vaccination schedule completion.

Conclusion: The experiential burden of under-five death within families and higher U5M at province-level was associated with lower completion of vaccination schedules in surviving children; however, indicators of under-five mortality risk likely overlap with other barriers to access for immunization services in surviving children. The shared root causes of childhood mortality and access to immunization services merits further investigation, particularly with respect to lower administrative levels of analysis.

Introduction

As of 2019, sub-Saharan Africa accounts for nearly 50% of the 19.7 million children worldwide who were reported to be under-vaccinated, comprising those who have received some, but not all, recommended vaccines or no vaccines at all.[1] For example, only 82% of infants born in Eastern and Southern Africa, and 76% in Central and West Africa were vaccinated at birth with BCG which is the first vaccine in the schedule and an important proxy for initiating immunization schedules.[2] Given these reports, the Global Vaccine Action Plan's target of achieving at least 90% coverage for all recommended childhood vaccines by the end of 2020, which was endorsed by governments across the sub-region, appears to be out of reach for most African nations.[3] With regional population growth estimated at 2.7% per year[4], the number of under-vaccinated and non-vaccinated children in sub-Saharan Africa is expected to grow

rapidly if new approaches and renewed investment are not identified to rapidly scale-up vaccination.

Increasing access to basic preventive health services such as immunization is key to improving childhood survival in sub-Saharan Africa[5–7], where children are 15 times more likely to die before age-five than in high-income countries.[8] In addition to sub-Saharan Africa having the lowest regional vaccination coverage of any other geographic regions worldwide, low vaccination coverage within countries in the region tends to be concentrated geographically and overlapping with other determinants that may predict elevated risk for premature death in childhood.[9,10] These so-called vulnerable populations on the aggregate are considered a priority for immunization outreach in operational and strategic plans both globally and regionally.[11,12] Nonetheless, childhood vaccination patterns among families and communities who have endured the experience of losing a young child have not been well-studied. Understanding whether exposure to premature childhood death during motherhood motivates vaccination choices or shows any association with vaccination outcomes for surviving children may be helpful for developing evidence-driven outreach and education to the populations deemed as a priority for strategic immunization activities.

Social and individual bereavement experiences and learning following the death of a young child is one of the most studied phenomena of countries undergoing demographic transitions, commonly cited as a driving determinant of subsequent health and fertility decisions at the individual level.[13] Applying this theoretical framing to high U5M settings early in their demographic transitions such as that of sub-Saharan Africa[14], bereaved parents, and community members, via learning from their social networks, might seek to improve survivorship of live births through increased utilization of health promotion activities[15] like immunization. However,

this contradicts the observed reality of low vaccination coverage persistently being a problem in geographic areas with an elevated risk of childhood mortality.[16] Another explanation for this pattern could be that the experience of losing a child prematurely is an indicator of other barriers to access. The direction of this relationship and whether it exists at all is best explored at an individual level, comparing vaccination outcomes among surviving children between families and communities who have differing levels of experience with under-five death.

Since 1984, the Demographic and Health Survey (DHS) has collected complete birth histories and childhood vaccination records from mothers sampled in participating countries.[17] As a highly utilized and standardized survey, the DHS has been one of the most important sources of data for evaluating predictors of immunization internationally.[17] This study uses recent DHS data from 33 sub-Saharan African countries to examine the relationship between the occurrence of under-five death among children born in the preceding 10-year period and vaccination outcomes in surviving children.

Methods

Data sources, study population and timeframe

DHS data was obtained from all SSA countries where a DHS survey was conducted between 2010-2019 (available as of 06/2020) (Table 3.1). Using a standardized household survey design approach across participating countries, the DHS partners with local institutions to collect nationally representative health and demographic data to inform health policy and program decision-making at national and global levels.[18] The sample design and survey methodology for this widely used data source has been thoroughly described elsewhere.[17] Briefly, the DHS employs a two-stage sampling procedure where sub-national geographic areas are chosen for inclusion using a probability of selection proportional to the area's population size and other

stratification characteristics. In the second stage, field workers generate a complete listing of households in the sampled areas and then systematically select 20-30 in each area for interviews.[19]

All women aged 15-49 from households selected for the survey are interviewed using an extensive questionnaire, which asks women about their health behaviors, contraceptive and reproductive preferences, health service utilization, and the survivorship and health of any children. Women also provide a complete birth history for up to 20 births. [20] For each live birth in the 3-5 years prior to the interview (with the time interval dependent on the country-specific adaption of the protocol), women report their children's vaccination status, including the number of vaccine doses and dates of administration for each up until the date of interview.[20,21]

Exposure to premature childhood death in a family over a 10-year period was defined by evaluating the women's complete birth histories. From the immunization records collected, vaccination outcomes were determined for surviving siblings who were 12-23 months at the time of the interview (index children). All index children who had no siblings, only younger siblings or siblings who were born more than 10 years prior to the interview were excluded. After linking sibling history to vaccination outcomes of index children, descriptive variables defining the order of relationship between the index child used for vaccination outcomes and any siblings were derived to sibships that met exclusion criteria. Finally, all but the oldest index child from multiple births or close interval births were excluded to avoid correlated outcomes among the small proportion of families who had more than one child aged 12-23 months at the time of interview.

To the authors' knowledge, no studies have used the DHS birth histories to construct a period-exposure of under-five death within a family on surviving siblings' vaccination outcomes.

Although one study[15] evaluating the association between preceding sibling death and maternal and child health services utilization was identified in the literature, there was no clear explanation provided for the decision to study only the preceding child's survival exposure. As an exploratory approach, the exposure period for this study was defined as the 10 years prior to interview, considering the potential influence of maternal recall bias beyond this time period.

Outcome

The primary outcome of interest was a dichotomized indication of receipt of all basic recommended vaccines by the time of interview, often referred to as up-to-date or fully immunized. For the present study, index children were considered fully immunized (FIC [fully immunized child]) if their vaccination record data indicated that they had received one dose of Bacillus-Calmette-Guerin (BCG), three doses of Oral polio vaccine (Polio) and 3 doses of the Pentavalent (Penta) combination vaccine (i.e. diptheria-tetanus-pertusis [DPT] – Hepatitis B [HepB] – Haemophilus influenzae type b [Hib]) and one dose of Measles-containing vaccine (MCV) prior to the interview occurring in the 12-23 month of age window The use of IPV in addition to OPV in low- and middle-income countries is a recommendation only from 2013, which falls in the middle of the decade selected for survey inclusion, and therefore this vaccine was not evaluated.[22]

Exposure to sibling death

Older sibling deaths in the prior 10-year period that occurred before 59 months of age i.e. age at death, were flagged. We chose to limit our study of the experience of child death on vaccination outcomes to death in the childhood period considering that any subsequent parental behavior changes to childhood vaccination would implicitly target survivorship under-five. Index children were assigned to the exposure category if at least one older sibling had died before the

age of five, and otherwise assigned as not exposed. Although the cumulative number of older sibling deaths per index child was tallied, any death experience in the exposure period was used as the initial exploratory exposure and the cumulative number of decedent older siblings was explored in sensitivity analysis.

Covariates

While it was not an aim to determine causal pathways in this exploratory analysis, there are several factors that may bias the association between childhood sibling death exposure and vaccination outcomes for the surviving sibling, some of which were unavailable in the DHS, described in the directed acyclic diagram available in Figure 3-1. Sociodemographic and economic factors at community or household-levels that were available in the DHS or using the authors' own construction were evaluated, such as household wealth, rural versus urban residence location, and 10-year under-five mortality (U5M) for the region of residence within each child's respective country. Household wealth quintiles were provided by DHS based on a household asset module and index construction via Principle Component Analysis (PCA). Rural versus urban geographic residence location was determined at the country-level. U5M at the level of each country's region/province was calculated over the exposure period of 10 years prior to the interview. Following DHS guidance[21], component probabilities of survival were estimated and then the conditional probability of survival by age five per 1000 live births was generated using DHS.rates package in R.[23] Finally, community-level exposure to underlying rates of childhood mortality was operationalized by converting the continuous U5M per 1,000 live births to quartile cut-offs in the distribution, creating a 4-level categorical variable: low (<64.5 per 1000 live births), low-medium (64.5-88 per 1000 live births), medium-high (89-125 per 1000 live births), and high (>125 per 1000 live births).

Mother-level covariates included educational attainment and maternal age at the woman's first birth. Educational attainment was categorized as none, primary, secondary or higher levels. The continuous measure of age at first delivery was converted to a categorical variable, grouping <15 years, 20-24 years, 25-29 years, and 30-44 years of age. Finally, the total number of children born in the 10 year exposure period was also considered.

Statistical analyses

The sample was described by stratifying covariates on the exposure to assess potential levels of confounding, which informed a purposeful approach to variable selection for inclusion in statistical models. Bivariate associations between all independent variables and the outcome were assessed. All variables showing a statistically significant association with the outcome at the level of <0.20 were considered for inclusion. Using a between mother analytical approach after restricting the sample to one index child per mother, the association between the sibling death exposure and vaccination outcome in the index child was estimated using binomial models with a logit link. Sequential and purposeful forward selection was used to adjust for observed confounding. Model 1 adjusted for household and higher-level variables; Model 2 adjusted for mother-level covariates; and Model 3 adjusted for child-level covariates. Joint F-tests and significance level for each set of covariate betas were considered to determine the overall suitability of the model to inform interpretation.[24]

Additionally, assessing the heterogeneity in the main effect across community-level experience with under-five death was explored to ascertain whether associations between under-five death in a family and vaccination outcomes in subsequent children varied across levels of U5M in the community, testing the hypothesis that the association of under-five death in a family and subsequent vaccination outcomes may be conditioned on the community level experience

with U5M. Lacking this type of information specifically in the DHS, we used the categorical derivation of U5M at the regional/province-level as a proxy for community exposure and interacted this variable with the primary exposure at the family-level. We reported adjusted Wald tests for interaction terms, and only maintain terms significant at the 0.05 alpha level.

All models controlled for unobserved confounding between countries using a dummy indicator term and using continuous variable for year of interview. Survey procedures were used to account for the stratified cluster sample design within each country, using the women's weights provided by DHS and re-weighting them to give equal weight to each country-year survey. All analyses were conducted in 08/2020 using Stata version 16 (Statacorp, LLC; College Station, TX).

Results

A total of 69,552 sampled children 12-23 months were assessed for vaccination status across 33 sub-Saharan African countries by DHS between 2010-2019. 16,922 children were excluded from this study after not meeting inclusion criteria (Figure 3-2). Among 52,687 children retained for the sample, the average age was 17.22 months, there were equal numbers of female and male children, and nearly 45% were only the 2nd or 3rd birth in the family (Table 3.2) Mothers of the children were predominantly young (56% aged 15-19; and 30% aged 20-24) at the time of their first birth, and lacked any education (44% reporting no formal education). The sample was characterized by more than two-thirds residing in rural areas, and nearly a quarter belonging to the poorest wealth quintiles (Table 3.2).

On average, children had 2.27 siblings who had preceded them in the prior 10-years in the family birth order, which was higher for families who had experienced an under-five death in the prior 10 years (mean 3.02, standard error 0.01). A total of 10,559 (20%) of children in the

sample were born to families who had experienced the premature death of at least one preceding child. A larger proportion of children born to families who had experienced a prior child death in the under-five period were 4th or higher birth order than children who had no prior sibling deaths. These children lived in rural areas in larger proportions (77% vs 67%), had mothers with greater levels of little to no formal education (85% vs 74%), and younger mothers at their first childbirth (<20: 67% vs 60%). Children born to families with prior young sibling death also were fully immunized at a lower proportion (51% vs 58%). Table 3-2 further describes the sample stratified on the main effect.

The models used to estimate the association between exposure to under-five death in a family (using the experience of death in siblings preceding the observed childhood vaccination outcomes) and subsequent surviving children being fully immunized provided varying absolute estimates of the relationship, but all associations suggested that experience with under-five death within families reduced the likelihood of surviving children being fully immunized. Model 1 (without any adjustment) estimated that the odds of being fully immunized (FIC) in children born to families who had experienced an under-five death in the previous 10-year period was .75 times the odds of being FIC for children without a prior sibling death (95%CI: 0.71-0.79). Adjusting for factors at the household and community-levels, and then adding mother-level covariates , the association was slightly attenuated and approaching the null, respectively, (Model 2 - aOR:0.88; 95%CI:0.78-0.97) and (Model 3 – aOR: 0.89; 95%CI:0.84-0.95). The final model adjusted for the number of older siblings, which showed a non-significant association, just crossing the null (aOR:0.94; 95%CI:0.88-1.01). All other adjusted associations are described in Table 3.3.

The likelihood of children being fully vaccinated in their early childhood among families who had experienced the premature death of a prior child did not significantly differ across strata of under-five mortality, after considering the potential for heterogeneity in the association by including an interaction term (*p* for interaction = 0.44; not shown). The variation in probability of being fully vaccinated associated with a prior sibling death across mortality strata was assessed qualitatively by plotting the average marginal effects and 95% confidence intervals (not shown). As was observed in testing the statistical significance of the interaction term, the confidence intervals were wide, overlapping between strata, and, except for the low-medium mortality strata, crossed the null. However, pooled U5M strata at the provincial level over the 10-year period prior to the survey was independently associated with vaccination outcomes in children sampled, revealing that children who resided in higher mortality strata areas were less likely to be fully vaccinated in early childhood (Model 3: low-medium vs low – aOR:0.89, 95%CI 0.81-0.97; medium-high vs. low – aOR:0.89, 95%CI 0.81-0.98; high vs low – aOR:0.80, 95%CI 0.71-0.90). In sensitivity analysis, the cumulative number of decedent siblings was tested for potentially being a more appropriate measure of U5M experience in a family, but the findings did not differ from the main analyses.

Discussion

Persistently high childhood mortality in the presence of low vaccination uptake within many communities in sub-Saharan Africa is a considerable obstacle for sustained improvement of childhood survival. At the end of 2015, the year which marked the conclusion of the Millennium Development Goals and an unprecedented global effort to improve childhood survival, nearly 25% of childhood deaths in sub-Saharan Africa were still due to causes potentially preventable by vaccination.[25] Characterizing vaccination patterns in families and

communities most afflicted by high U5M is urgently needed to understand how to adapt education and outreach in the years ahead as countries work towards reducing childhood mortality to fewer than 25 under-five deaths per 1,000 live births, in accordance with the updated global health goals stated in the 2030 Sustainable Development Goal (SDG) Agenda. In this regard, the impact of child mortality within a family and community on parents' subsequent preventive health service seeking behavior for their surviving children is an under-studied pathway for targeting interventions that may help improve vaccination among the most vulnerable populations.

To the authors' knowledge, this study is the first to compare vaccination outcomes among families who have experienced the premature loss of a child to families with no prior history of childhood death. We found that after adjusting for factors that are known to influence vaccination behavior and access, the likelihood of children being fully vaccinated following a premature death among older siblings in the family did not differ significantly from children with no prior sibling deaths; however, the confidence interval for the association only barely crossed the null after controlling for the number of siblings and otherwise the estimated associations showed that the experience of childhood death was associated with poor vaccination outcomes in surviving children. We also found that families residing in areas with a higher probability of under-five death were significantly less likely to have their children fully vaccinated compared to families living in the lowest U5M burden areas.

This study was initially motivated by a supposition that parents, caretakers, or community leaders may change their risk-benefit calculation of health decisions following direct experience with a child dying in early life due to a desire to make assurances about their surviving children's continued survivorship. However, this hypothesis assumes families and communities have no

other barriers to accessing immunization services following a shift in risk perception or motivation that changes care-seeking behaviors that we know does not hold. It also presupposes that the experience of childhood death in a family would motivate differential vaccination uptake in surviving children. Residing in higher U5M strata at the sub-national level was predictive of worse vaccination outcome, which suggests that clustering of under-five death shares a bi-directional relationship with access disadvantages.

This complicates any program's outreach targeting strategies when children who are at-risk share socioeconomic, geographic, or other access disadvantage that are predictive of barriers to immunization, which further contributes to concentrating the risk of under-or non-vaccination. Sibling death as a determinant of maternal health service utilization in subsequent pregnancies was explored in a Nigerian study, where no association was found after similarly controlling for other predictive factors of access.[15] Although the authors used a similar approach to ours, decisions that women make about their own health may be affected differently from child death than decisions they make on behalf of their surviving children. In Kenya, researchers assessed predictors for infant influenza vaccination as an important preventive health service, including history of hospital admission or death of a sibling under-five in the year preceding the vaccination campaign.[26] In contrast to our evidencing of a direction of relationship, though non-significant, that suggests experience of child death is a barrier to favorable vaccination outcomes in surviving siblings, Otieno et al. 2014 found that children of families with a history of sibship hospitalization (AOR: 1.73; 95%CI 1.40-2.14) or death (AOR:1.48; 95%CI0.74-2.96) were more likely to receive influenza vaccine during the campaign than their comparator, findings that are line with our initial hypothesis. One explanation for the difference in their findings from those observed in our study could be that Otieno et al. 2014 assessed respiratory associated hospital

admission and death exposure as opposed to any cause. Had information on the cause of under-five death been available to us, we might have observed a stronger positive response in vaccination outcomes following a death in the family associated with vaccine-preventable causes.

Several countries in the sub-region have established health and demographic surveillance systems to track vital statistics and other health indicators in vulnerable populations.[27] Using platforms such as INDEPTH that allow for prospective follow-up, the study of associations between sibling death or community concentration of under-five mortality and near-term health behaviors could help clarify the utility of tracking infant and child deaths in a family as a risk factor for uptake of vaccination. Other cohort studies in high-income settings, such as Scandinavia, have found a 1.7 to 2-fold increase in instantaneous mortality risk for individuals who experience the death of a sibling in early childhood.[28] However, the mechanisms for the increased risk of death following exposure to a sibling death were not studied. Future studies might also consider collecting data on changes in parental perceptions of vaccination and other health service utilization to allow for more precise study of the parent/caretaker effect on health seeking behavior on behalf of their surviving children following the death of preceding children. There has been recent attention to the consideration of the concentrated effect of childhood mortality on health and wellbeing outcomes in Africa, by assessing under-five mortality from the perspective of the bereaved mother or community instead of spreading the experience across families and communities who have not experienced child death with the typical probability of survival measures.[29] A recent methodological paper published an approach to considering the cumulative bereavement exposure during a mother's lifetime by estimating the maternal cumulative prevalence of under-five mortality.[30] These measures may more precisely capture the

community exposure bereavement that was intended with the use of sub-national U5M in this paper. To further understand the determinants of vaccination among families and communities who have experienced death of their children, we might consider how the magnitude of association changes across socioeconomic strata in place of confounder adjustment. This might help strengthen the hypothesis that U5M represents an indicator for disadvantage to accessing health services. Similarly, we could also consider evaluating how premature death of a child within a shorter time interval prior to the vaccination status assessment of surviving children changes compared to the interval of 10 years used in this study. If the direction and magnitude of the association are unchanged with the shorter exposure interval, we would assume that childhood death, even following an acute bereavement period, indicates disadvantage to accessing immunization services. This latter approach also would more appropriately control for temporal changes to socioeconomic status that are not observed between a prior childhood death and the wealth status captured at the time of interview.

There are several limitations to this study. Proxy measures for community and family risk of under-five death were identified in the data available, which may not be suitable units of analysis for children who do not live in the same household as their preceding siblings who died or where administrative provinces represent artificial divisions of risk. In this sense, misclassification of exposure assignment to sibling/community under-five death could have biased the associations. Considering spatial coordinate data in future analyses would be helpful. Secondly, the cause of death for children in the DHS is unknown. While causes of death associated with illness that can be preventable with vaccines is still very common in SSA (e.g., diarrhea, bacterial pneumonia and sepsis, measles), the distribution of death causes for siblings identified in this study could skew differently. In this sense, the associations may have been more obvious if analysis were

restricted to only deaths associated with infectious causes especially those which were vaccine-preventable. Finally, owing to the cross-sectional data source, time-varying confounders were not available. However, the temporal ordering of a sibling death prior to observing vaccination outcomes in subsequent children was achieved with the use of complete birth histories collected by the DHS.

Conclusion

The experiential burden of under-five death within families and higher U5M at province-level was associated with lower completion of vaccination schedules in surviving children. However, indicators of under-five mortality risk likely overlap with other barriers to access for immunization services in surviving children. The shared underlying determinants of childhood mortality and access to immunization services merits further investigation, which may be more feasible to study ecologically using geospatial data at lower administrative levels or considering longitudinal follow-up of families and communities that have high experiential burden of under-five mortality.

Table 3.1 List of Demographic and Health Surveys and country characteristics for sample, sub-Saharan Africa, 2010-2019

Country	Survey year	Survey[a] sample	Meet criteria[b]	% sample used	% by country	Fully immunized[c]	U5M (per 1000 livebirths)[d]
Angola	2015-16	2,845	2,183	77%	4.1%	28.6%	68
Burkina Faso	2010	2,790	2,238	80%	4.2%	81.3%	129
Benin	2017-18	2,522	1,912	76%	3.6%	55.7%	96
Burundi	2016-17	2,596	2,086	80%	4.0%	84.9%	78
Congo Dem. Republic	2013-14	3,438	2,709	79%	5.1%	44.3%	104
Congo	2011-12	1,883	1,397	74%	2.7%	39.1%	68
Cote D'Ivoire	2011-12	1,416	1,050	74%	2.0%	50.2%	108
Cameroon	2011	2,278	1,682	74%	3.2%	50.5%	122
Ethiopia	2016	1,929	1,471	76%	2.8%	36.8%	67
Gabon	2012	1,187	853	72%	1.6%	6.4%	65
Ghana	2014	1,128	837	74%	1.6%	79.7%	60
Gambia	2013	1,645	1,245	76%	2.4%	78.4%	54
Guinea	2018	1,408	1,095	78%	2.1%	22.4%	111
Kenya	2014	4,048	3,003	74%	5.7%	70.3%	52
Comoros	2012	626	464	74%	0.9%	62.0%	50
Liberia	2013	1,432	1,078	75%	2.0%	50.6%	94
Lesotho	2014	655	360	55%	0.7%	66.3%	85
Mali	2018	1,946	1,559	80%	3.0%	43.9%	101
Malawi	2015-16	3,248	2,333	72%	4.4%	75.1%	64
Mozambique	2011	2,225	1,655	74%	3.1%	62.8%	97
Nigeria	2018	6,059	4,796	79%	9.1%	29.7%	132
Niger	2012	2,147	1,808	84%	3.4%	50.8%	127
Namibia	2013	991	636	64%	1.2%	71.6%	54
Rwanda	2014-15	1,536	1,073	70%	2.0%	41.5%	50
Sierra Leon	2013	2,083	1,561	75%	3.0%	67.5%	156
Senegal	2017	2,390	1,774	74%	3.4%	74.5%	56
Chad	2014-15	2,870	2,454	86%	4.7%	24.9%	133

Togo	2013-14	1,404	1,019	73%	1.9%	59.3%	88
Tanzania	2015-16	2,158	1,571	73%	3.0%	73.0%	67
Uganda	2016	2,922	2,189	75%	4.2%	55.5%	64
South Africa	2016	670	380	57%	0.7%	60.9%	42
Zambia	2018-19	1,926	1,422	74%	2.7%	74.4%	61
Zimbabwe	2015	1,151	794	69%	1.5%	74.9%	69

a: Total number of children 12-23 months at time of interview in each nationally representative sample; **b:** Total number of child observations in country survey samples identified as (1) having vaccination records by review of vaccine cards or maternal recall, and (2) having a preceding sibling born within 10-years of the survey date; **c:** Proportion of children who meet study inclusion criteria that are fully immunized, defined as having record of all 8 basic vaccinations by the time of interview (maternal recall or vaccine card review) in the DHS, adjusted for survey design; **d:** U5M = Under-five mortality at national-level during the 10-year period prior to survey interviews, calculated using DHS birth histories and adjusted for survey design.

Table 3.2 Distribution of characteristics of children 12-23 months sampled in included DHS surveys, sub-Saharan Africa, 2010-2019. Unweighted frequencies and weighted proportions/means for all covariates, using country-specific DHS weights

	All children	Prior sibling death	No prior sibling death
	n=52,687	n=10,559	n=42,128
	*Unweighted frequencies (weighted %) or *Weighted Mean (SE)*		
Index child's age, months*	17.22 (0.02)	17.24 (0.05)	17.22 (0.02)
Sex			
Male	26,536 (50.0%)	5,319 (49.3%)	21,217 (50.4%)
Female	26,239 (50.0%)	5,345 (50.7%)	20,894 (50.6%)
# older siblings born in prior 10 years*	2.27 (0.01)	3.02 (0.02)	2.09 (0.01)
Birth order rank			
2nd-3rd	23,513 (45.9%)	2,717 (26.9%)	20,796 (50.6%)
4th-6th	20,413 (38.1%)	5,019 (45.7%)	15,394 (35.9%)
7th +	8,761 (16.0%)	2,823 (26.4%)	5,938 (13.4%)
Maternal age at first birth			
<15	3,528 (6.6%)	957 (9.3%)	2,571 (5.9%)
15-19	29,584 (55.6%)	6,254 (58.2%)	23,330 (54.9%)
20-24	15,677(30.2%)	2,806(27.5%)	12,871 (30.9%)
25-29	3,247 (6.4%)	452 (4.3%)	2,795 (6.9%)
30-45	651 (1.3%)	90 (1.0%)	561 (1.4%)
Maternal education			
None	23,140 (43.7%)	5,606(53.9%)	17,534 (41.2%)
Primary	18,178 (32.9%)	3,438 (31.1%)	14,749 (33.4%)
Secondary	10,164 (21.0%)	1,417(14.1%)	8,747 (22.8%)
Higher	1,200 (1.3%)	97 (1.0%)	1,103 (2.7%)
Residence type			
Rural	37,851 (69.1%)	8,361 (77.4%)	29,490 (67.0%)
Urban	14,924 (30.9%)	2,303 (22.6%)	12,621 (33.0%)
Household wealth			
Poorest	14,208 (24.0%)	3,283 (28.9%)	10,925 (22.7%)
Poorer	11,877 (22.3%)	2,616 (24.9%)	9,261 (21.8%)
Middle	10,494 (20.3%)	2,101 (20.2%)	8,393 (20.4%)
Richer	8,956 (18.7%)	1,597 (16.3%)	7,359 (19.3%)

Richest	7,152 (14.7%)	962 (9.9%)	6,190 (15.9%)
Under-five mortality, regional residence			
Low	13,143 (25.6%)	1,569 (14.9%)	11,574 (28.3%)
Medium-low	13,107 (24.4%)	1,981 (18.2%)	11,126 (25.9%)
Medium-high	13,118 (25.5%)	2,779 (27.3%)	10,339 (25.0%)
High	13,319 (24.5%)	4,230 (39.6%)	9,089 (20.1%)

Table 3.3 Logistic regression results for assessing the association between under-five death in preceding children over a 10-year period and vaccination outcomes in surviving siblings. Pooled analysis in 33 DHS countries, 2010-2019

	Model 1 (unadjusted)	**Model 2** (adjusted, geo-social)	**Model 2** (adjusted, geo-social + mother)	**Model 3** (adjusted, geo-social + mother + child)
	Odds Ratios (ORs) comparing odds of fully immunized status in children with and without prior sibling death, (95% Confidence Intervals)			
Sibling death in prior 10 years				
No	ref	Ref	Ref	Ref
Yes	**0.75 *** (0.71-0.79)**	**0.88 *** (0.78-0.97)**	**0.89 *** (0.84-0.95)**	**0.93 (0.87-1.00)**
Residence location				
Urban		Ref	Ref	Ref
Rural		1.05 (0.97-1.14)	1.08 (0.99-1.18)	1.09 (1.00-1.19)
Under-five mortality, regional level				
Low (1st quartile)		Ref	Ref	Ref
Low-Medium (2nd quartile)		0.88 ** (0.80-0.96)**	0.88 ** (0.81-0.97)	0.88 ** (0.81-0.97)
Medium-High (3rd quartile)		0.88 ** (0.79-0.97)	0.89 * (0.81 - 0.99)	0.89 * (0.81-0.98)
High (4th quartile)		0.77 *** (0.68-0.16)	0.80 *** (0.71-0.89)	0.80 *** (0.71-0.90)
Household wealth				
Poorer		Ref	Ref	
Poor		1.30 *** (1.21-1.40)	1.26 *** (1.17-1.35)	1.25 *** (1.16-1.35)

		1.59 ***	1.49 ***	1.47 ***
Middle		(1.46-1.71	(1.37-1.60)	(1.36-1.59)
		1.83 ***	1.66 ***	1.63 ***
Rich		(1.66-1.99)	(1.51-1.81)	(1.49-1.79)
		2.20 ***	1.83 ***	1.79 ***
Richer		(1.96-2.45)	(1.62-2.05)	(1.59-2.01)
Maternal education				
None			ref	Ref
			1.29 ***	1.29 ***
Primary			(1.20-1.39)	(1.19-1.38)
			1.61 ***	1.60 ***
Secondary			(1.46-1.77)	(1.45-1.76)
			1.71 ***	1.69 ***
Higher			(1.32-2.20)	(1.32 - 2.18)
Maternal age (at first child birth)				
<15 years				Ref
			1.26 ***	1.27 ***
15-19 years			(1.14-1.39)	(1.14-1.40)
			1.35 ***	1.36 ***
20-24 years			(1.21-1.50)	(1.22-1.52)
			1.27 **	1.29 **
25-29 years			(1.09-1.48)	(1.11 - 1.50)
			1.29 *	1.32 *
30-45 years			(1.01 - 1.64)	(1.03-1.68)
Older siblings born, continuous				0.89 ***
				(0.86-0.93)
Year, continuous	yes	yes	yes	yes
Country, indicator categorical	yes	yes	yes	yes
Observations	52,687	52,687	52,687	52,687

* p<0.05; ** p<0.01; p<0.001

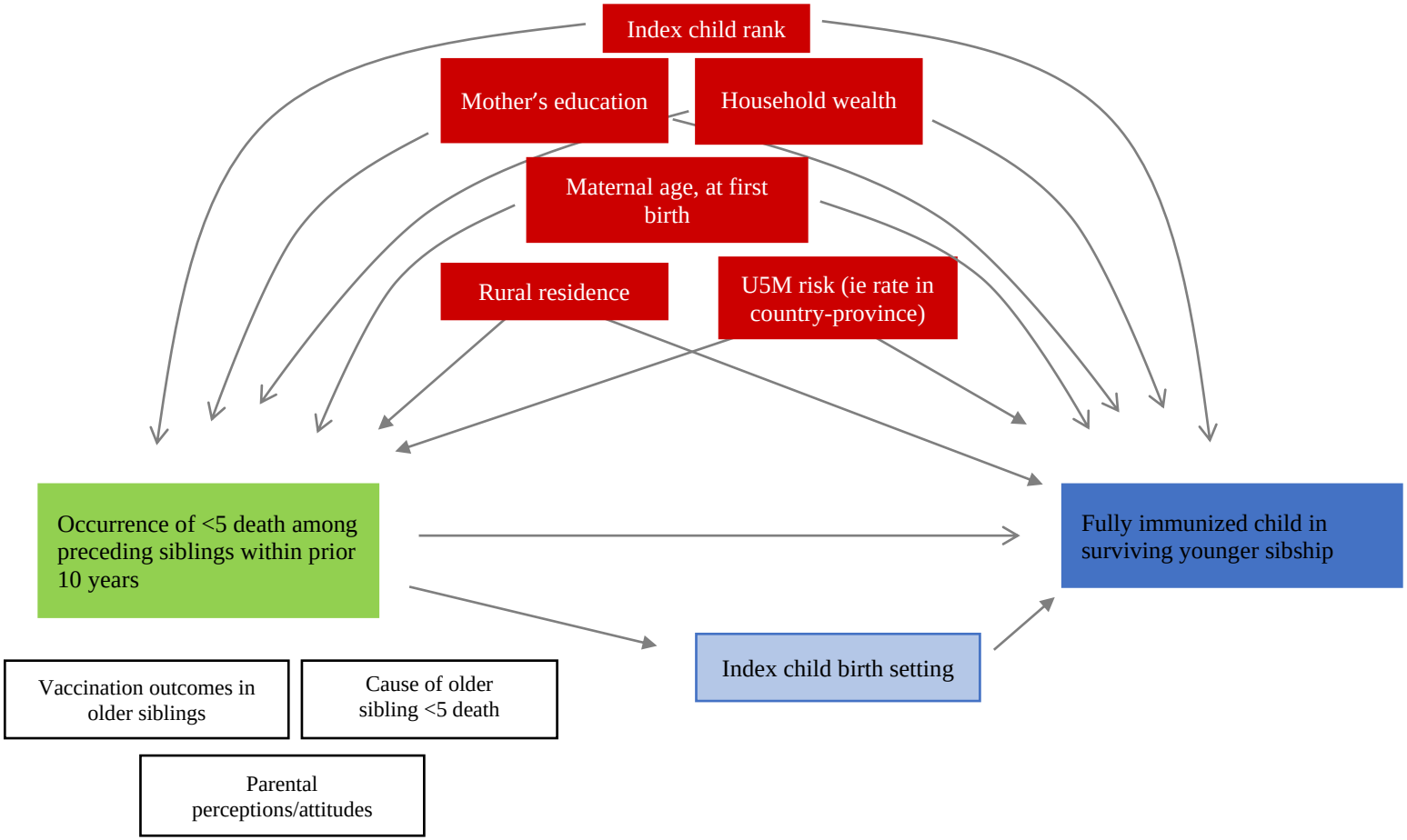

Figure 3-1 Direct Acyclic Diagram for evaluating the relationship between under-five childhood death and vaccination outcomes in surviving siblings within families

This DAG represent the hypothesized relationships between the main predictor variable (in green) and the outcome (in dark blue), while considering other observed confounders (in red), representing unobserved confounders (in white) anexposure variables that may

play a mediated role in the overall effect (in light blue). Thevariables in light blue were excluded from the analysis. Variables in white were not available for consideration in the analysis, which represent a limitation.

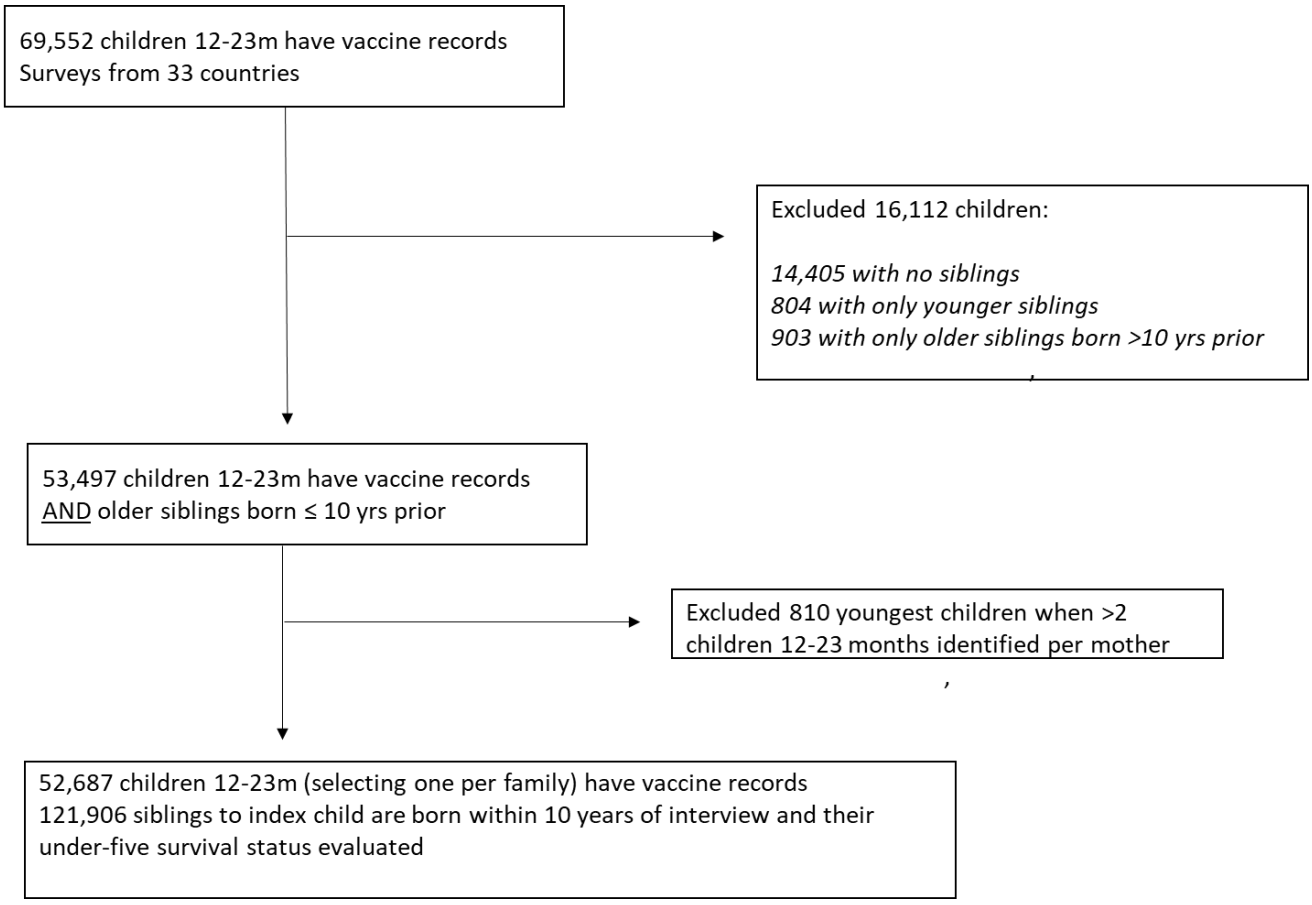

Figure 3-2 Flow diagram of sample selection for assessing the relationship between under-five childhood death over a 10-year period and vaccination outcomes of surviving siblings

References

1. The Strategic Advisory Group of Experts (SAGE). *GVAP 2011-2020, Review and Lessons Learned*.; 2020. https://apps.who.int/iris/bitstream/handle/10665/329097/WHO-IVB-19.07-eng.pdf?ua=1.

2. WHO. *WUENIC Estimates, 2020*.; 2020. https://www.who.int/immunization/monitoring_surveillance/data/en/.

3. MacDonald N, Mohsni E, El-Mazrou Y, et al. Global vaccine action plan lessons learned I: Recommendations for the next decade. *Vaccine*. 2020;14(38):5364-5371.

4. World Bank. World Development Indicators DataBank. https://databank.worldbank.org/. Published 2020. Accessed January 10, 2020.

5. McGovern ME, Canning D. Vaccination and All-Cause Child Mortality From 1985 to 2011: Global Evidence From the Demographic and Health Surveys. *Am J Epidemiol*. 2015;182(9):791-798. doi:10.1093/aje/kwv125

6. Fotso JC, Ezeh AC, Madise NJ, Ciera J. Progress towards the child mortality millennium development goal in urban sub-Saharan Africa: The dynamics of population growth, immunization, and access to clean water. *BMC Public Health*. 2007;7:1-10. doi:10.1186/1471-2458-7-218

7. Kristensen I, Aaby P, Jensen H. Routine vaccinations and child survival: Follow up study in Guinea-Bissau, West Africa. *Br Med J*. 2000;321(7274):1435-1439. doi:10.1136/bmj.321.7274.1435

8. You D, Hug L, Ejdemyr S, et al. Global, regional, and national levels and trends in under-5 mortality between 1990 and 2015, with scenario-based projections to 2030: A systematic analysis by the un Inter-Agency Group for Child Mortality Estimation. *Lancet*. 2015;386(10010):2275-2286. doi:10.1016/S0140-6736(15)00120-8

9. Brownwright TK, Dodson ZM, Van Panhuis WG. Spatial clustering of measles vaccination coverage among children in sub-Saharan Africa. *BMC Public Health*. 2017;17(1):1-7. doi:10.1186/s12889-017-4961-9

10. Melaku MS, Nigatu AM, Mewosha WZ. Spatial distribution of incomplete immunization among under-five children in Ethiopia: Evidence from 2005, 2011, and 2016 Ethiopian Demographic and health survey data. *BMC Public Health*. 2020;20(1):1-22. doi:10.1186/s12889-020-09461-3

11. Ryman T, MacAuley R, Nshimirimana D, Taylor P, Shimp L, Wilkins K. Reaching every district (RED) approach to strengthen routine immunization services: Evaluation in the African region, 2005. *J Public Health (Bangkok)*. 2010;32(1):18-25. doi:10.1093/pubmed/fdp048

12. Ozawa S, Yemeke TT, Evans DR, Pallas SE, Wallace AS, Lee BY. Defining hard-to-reach populations for vaccination. *Vaccine*. 2019;37(37):5525-5534. doi:10.1016/j.vaccine.2019.06.081

13. Sandberg J. Infant Mortality , Social Networks , and Subsequent Fertility Author (s):

John Sandberg Published by : American Sociological Association Stable URL : https://www.jstor.org/stable/30038989 Infant Mortality , Social Networks , and Subsequent Fertility. 2006;71(2):288-309.

14. Bongaarts J, Casterline J. Fertility Transition: Is sub-Saharan Africa Different? *Popul Dev Rev*. 2013;38(SUPPL.1):153-168. doi:10.1111/j.1728-4457.2013.00557.x

15. Akinyemi JO, Bolajoko I, Gbadebo BM. Death of preceding child and maternal healthcare services utilisation in Nigeria: Investigation using lagged logit models. *J Heal Popul Nutr*. 2018;37(1):1-12. doi:10.1186/s41043-018-0154-0

16. Sartorius B, Cohen C, Chirwa T, Ntshoe G, Puren A, Hofman K. Identifying high-risk areas for sporadic measles outbreaks: lessons from South Africa. *Bull World Health Organ*. 2013;91(3):174-183. doi:10.2471/BLT.12.110726

17. Corsi DJ, Neuman M, Finlay JE, Subramanian S V. Demographic and health surveys: A profile. *Int J Epidemiol*. 2012;41(6):1602-1613. doi:10.1093/ije/dys184

18. ICF International. The DHS Program: Who We Are. https://www.dhsprogram.com/Who-We-Are/About-Us.cfm. Published 2020. Accessed April 20, 2020.

19. ICF International. *Demographic and Health Survey Sampling and Household Listing Manual*. Calverton, Maryland, USA; 2012.

20. ICF International. *Standard Recode Manual for DHS 6*. ICF International/MEASURE DHS; 2013.

21. Croft TN, Marshall AMJ, Allen CK. *Guide to DHS Statistics, DHS-7*. Rockville, Maryland, USA; 2018. http://www.measuredhs.com/pubs/pdf/DHSG1/Guide_to_DHS_Statistics_29Oct2012_DHSG1.pdf%5Cnhttp://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.431.8235&rep=rep1&type=pdf.

22. Patel M, Zipursky S, Orenstein W, Garon J, Zaffran M. Polio endgame: The global introduction of inactivated polio vaccine. *Expert Rev Vaccines*. 2015;14(5):749-762. doi:10.1586/14760584.2015.1001750

23. Elkasabi M. Calculating fertility and childhood mortality rates from survey data using the DHS.rates R package. *PLoS One*. 2019;14(5):1-22. doi:10.1371/journal.pone.0216403

24. Archer KJ, Lemeshow S. Goodness-of-fit test for a logistic regression model fitted using survey sample data. *Stata J*. 2006;6(1):97-105. doi:10.1177/1536867x0600600106

25. Liu L, Oza S, Hogan D, et al. Global, regional, and national causes of under-5 mortality in 2000–15: an updated systematic analysis with implications for the Sustainable Development Goals. *Lancet*. 2016;388(10063):3027-3035. doi:10.1016/S0140-6736(16)31593-8

26. Otieno NA, Nyawanda BO, Audi A, et al. Demographic, socio-economic and geographic determinants of seasonal influenza vaccine uptake in rural western Kenya, 2011. *Vaccine*. 2014;32(49):6699-6704. doi:10.1016/j.vaccine.2013.10.089

27. Ye Y, Wamukoya M, Ezeh A, Emina JBO, Sankoh O. Health and demographic surveillance systems: A step towards full civil registration and vital statistics system in sub-Sahara Africa? *BMC Public Health*. 2012;12(1):1. doi:10.1186/1471-2458-12-741

28. Yu Y, Liew Z, Cnattingius S, et al. Association of mortality with the death of a sibling in childhood. *JAMA Pediatr*. 2017;171(6):538-545. doi:10.1001/jamapediatrics.2017.0197

29. Weitzman A, Smith-Greenaway E. The Marital Implications of Bereavement: Child Death and Intimate Partner Violence in West and Central Africa. *Demography*. 2020;57(1):347-371. doi:10.1007/s13524-019-00846-7

30. Smith-Greenaway E, Trinitapoli J. Maternal cumulative prevalence measures of child mortality show heavy burden in sub-Saharan Africa. *Proc Natl Acad Sci U S A*. 2020;117(8):4027-4037. doi:10.1073/pnas.1907343117

Chapter 4 New Vaccine Introduction and Childhood Vaccination Timeliness in Two Urban Informal Settlements in Nairobi, Kenya

Abstract

Introduction: New vaccine introduction accompanied by social mobilization activities could contribute to improved routine immunization timeliness. This study assesses the impact of Kenya's introduction of PCV on the timeliness of routine childhood vaccination in two informal urban settlements in Nairobi.

Methods: Data collected from 2003-2015 as part of a demographic surveillance system was used to estimate annual vaccination delays among children 12-23 months of age in the period before and after the introduction of PCV in the Kenyan Expanded Programme on Immunization. Binomial segmented regression models using generalized estimating equations examined the association between vaccine introduction and timeliness of routine immunization.

Results: Over 50% of children in the two urban areas were vaccinated with 1 or more doses after the recommended age period from 2007-2015. The timeliness of routine immunization showed slight improvements or non-significant changes during the years following PCV introduction compared to the preceding years (adjusted Prevalence Ratio [aPR]: 0.67, 95% Confidence Interval [95%CI]: 0.45-0.99 for BCG receipt; aPR: 0.59, 95%CI: 0.41-0.83 for DPT3 receipt; aPR: 1.19, 95%CI: 0.99-1.42 for Measles). Delayed vaccination was still prevalent in 2015, particularly among the poorest residing in the settlements.

Conclusions: Many sub-Saharan African countries have introduced new vaccines into their routine immunization schedules, which have the potential to substantially reduce childhood

mortality. Additional evidence regarding the positive or neutral influence of new vaccine introduction on the performance of delivery systems provides further justification to sustain the inclusion of these more costly vaccines in the immunization schedule.

Introduction

Over the past two decades, the development and broad adoption of new childhood vaccines has resulted in remarkable improvements in child health. [1] However, at the time of their introduction into the global market, new vaccines were prohibitively expensive for low-and-middle income countries (LMIC), resulting in substantial lags in their adoption compared to in wealthier countries .[2] Additionally, new vaccine introduction implies other financial burdens on ministries of health such as upgrading outdated or strained immunization program infrastructure, improving surveillance systems, and investing in training and planning for safe and effective delivery strategies .[3] Despite these considerable financial and logistical obstacles, the lag in implementing new vaccine offerings has diminished in recent years for many parts of sub-Saharan Africa (SSA).[4]

The principle priority of contemporary immunization programs is achieving and maintaining high-levels of uptake for all childhood vaccines, many of which are critical to disease control and elimination efforts.[5] Effective protection against these diseases requires uniformly high levels of coverage in target populations at recommended age intervals, achieving 'on-time' vaccination.[6] That is, vaccines delivered too early may not confer adequate levels of long-lasting protection and vaccines delivered too late may result in unnecessarily prolonged periods for which children are at-risk of more serious illness or death from vaccine-preventable diseases.[7,8] With the inclusion of new vaccines into routine programs, immunization schedules

have become more complex and vaccination programs potentially more strained, which may negatively influence the performance of routine immunization services. Nonetheless, social mobilization, outreach, and information campaigns that often accompany the launch of new vaccines may positively influence routine immunization services, specifically creating synergies between the newly introduced vaccines and others already in the schedule around the overall timeliness of vaccination receipt.

Among the most rapidly developing economies in SSA, Kenya has made immunizations a health priority, introducing new vaccines ahead of many other LMICs, such as pneumococcal conjugate vaccine (PCV), in 2011, and rotavirus vaccine (RV), in 2014.[9] The Kenyan Expanded Programme on Immunization (KEPI) was established in 1980 by the Ministry of Health to provide vaccinations and monitor vaccine-preventable childhood illness and death. As of 2020, the routine childhood immunization schedule provided by KEPI includes one dose each of Bacille Calmette-Guerin (BCG) and Oral Polio Vaccine (OPV) at birth; three doses each of Diptheria – Tetanus – wPertussis - Haemophilus Influenzae Type B [Hib] - Hepatitis B [HepB] (Pentavalent), OPV and PCV at 6, 10 and 14 week; two doses of RV at 6 and 10 weeks; one dose of Inactivated Polio Vaccine (IPV) at 14 weeks; and two doses of Measles and rubella (MR) at 9 and 18 months of age.

Though specific to only a few settings, qualitative research on the health systems impact of new vaccine introduction has suggested existing challenges to chronically underfunded health systems and programs may be exacerbated, such as overextending the limited number of healthcare workers with new vaccine promotion activities and as a result unintentionally detracting from other high priority disease elimination goals.[3,10] By contrast, other research has found that the adoption of new vaccines was perceived as an opportunity to retrain and

strengthen healthcare workforce capacity and to further promote the benefit of immunization services as a whole, leveraging the availability of additional government resources or donor funding[11–13]. To date, few studies have quantitatively assessed the influence of new vaccine introduction on immunization program outcomes. Of those published[14–18], none are specific to Kenya's experience with recent new vaccine introduction in urban poor contexts. In this study, we describe and explore the potential impact of new vaccine introduction, using the experience of PCV as an example, on the timing of other vaccines recommended for routine use in two vulnerable, urban poor communities in Nairobi, Kenya. Using data from the Nairobi Urban Health and Demographic Surveillance System, we cross-sectionally assess annual trends in vaccination delays for routine immunization doses recommended at birth (BCG), 6, 10, 14 weeks (Pentavalent [Penta] and OPV) and 9 months (Measles) of age among children residing in the surveillance areas located in Viwandani and Korogocho, urban informal settlement communities within Nairobi, before and after the introduction of PCV.

Methods

Study setting: The Nairobi Urban Health and Demographic Surveillance System

The Nairobi Urban Health and Demographic Surveillance System (NUHDSS) was established to study the health effects of migration and poverty in the urban capital of Kenya. Managed by the African Population and Health Research Center (APHRC), the NUHDSS monitors health and demographic trends through the registration of all births, migratory movements, and deaths in two informal settlement communities, Korogocho and Viwandani, that were selected as examples of the diverse experience of slum-dwelling in Nairobi.[19] Circular migratory patterns between rural Kenya and Nairobi are common in both settings, though Korogocho has developed into a more stable and settled population. Households in Korogocho

are generally characterized by spousal co-residence and multi-generations of families that relocated from rural areas of Kenya beginning in the 1960s. In contrast, Viwandani's proximity to neighboring industrial areas attracts younger household heads, often settling temporarily without their entire family units, and fewer than 5% of residents are born in the settlement.[20,21] Violence coupled with absent security measures, poor or lacking infrastructure for sanitation, and governance issues related to land ownership disputes pose serious challenges to improving the health and wellbeing of the populations residing in both communities.[19,22] APRHC and partner agencies have used data from the NUHDSS to inform policy and programmatic changes that aim to improve the living conditions and health situation in Viwandani, Korogocho and other slums of Nairobi.[23]

All household units occupying dwellings in Korogocho and Viwandani were recruited for participation beginning in 2002. Since then, community interview teams staffed and trained by APHRC have visited the surveillance catchment every 120 days to update the surveillance system's register of participating residents, removing individuals who have out-migrated or died and incorporating births and individuals who have in-migrated. At recruitment, demographic and migration pattern data are collected for each member of the household and then information is collected on in- and out-migration, births, deaths, maternal and child health, and economic and food security during subsequent field interview visits.[19,21] As of 2018, the NUHDSS monitors 88,974 individuals who reside in 33,462 households in Viwandani and Korogocho and every year approximately 1,500 to 1,900 new live births are registered in the surveillance system.[24]

Study population sample: Children 12-23 months followed in the NUHDSS

As part of the maternal and child health focus of the system, the NUHDSS collects a record of vaccination for all children under-five who reside in the surveillance catchment.

Mothers or caretakers to age-eligible children provide a complete history of vaccination, and interviewers review card documentation to verify the date and number of doses for each vaccine received. Vaccination status is updated in the surveillance system for each child at every subsequent visit until the schedule is completed or the child is no longer age-eligible. Data on children aged 12-23 months at the time of interview was used for all publicly accessible years of surveillance data: 2003-2015. To reduce selection bias that may result from loss to follow up or survivorship during the 12-23 month period, the first vaccination record created in the system following 12 months of age was included for analysis. Vaccination records were matched to demographic data for each child and their households collected for the same year. Children who never had a vaccination card reviewed or who did not have a card available in the 12-23 month period were excluded from analysis.

Variables

The primary outcome was a binary variable of delayed versus on-time vaccination relative to the age-specific recommendations for vaccination at birth, 6 weeks, 10 weeks, 14 weeks and 9 months of age in Kenya for all vaccines recommended prior to the introduction of new vaccines (Table 4.1). Vaccination records that reported age at vaccination before the child's birthdate or other implausible vaccination dates, e.g. measles vaccination at birth, were excluded from analysis. Delays were defined as any vaccine dose that was administered four or more weeks after the recommended age of vaccination (Table 4.1). All vaccines administered within the time interval between the recommended age and the four-week delay window were considered acceptable timing for receipt and defined as on-time. Vaccination series completion, defined as receipt of all recommended vaccines by the age of 12 months, and dose-specific completion were also variables derived for descriptive analysis. Data on the child's sex, age,

ethnicity, and household wealth status were directly obtained from residency records. There was incomplete information in the system to identify all mother-child pairs, and therefore mother characteristics were not examined in this analysis.

Analysis

The distribution of demographic characteristics and vaccination status of children was explored over time, distinguishing between the before and after PCV introduction periods of the KEPI. The proportion of children who were delayed in their vaccination schedules was examined descriptively across three periods: 1) prior to PCV introduction (2007-2010), 2) during the year in which PCV was introduced (2011), and, 3) the period following PCV introduction (2012-2015). To explore the influence of new vaccine introduction on the dose-specific timeliness of routine immunization, segmented binomial regression using generalized estimating equations was used comparing the pre-introduction period (2007-2010) to the post-introduction period (2012-2015). To maintain balance in the period comparisons, only data from four years before and after the introduction of PCV were used in the models. Acknowledging the limited data availability to control for potential time-dependent confounders, we only sought to explore the association in terms of a time-dependent level change as opposed to changes in the trend trajectory, or slope defining the estimated prevalence of delayed vaccination receipt over time. Prevalence ratios reflecting pre- and post-introduction period level changes with robust standard errors were calculated, accounting for correlation due to approximately 30% of children residing in the same household unit as other families with children in the sample. Models included a term to control for annual trends in the outcome, given changes to the annual age-eligible catchment sample. Individual level factors that were hypothesized to influence the timeliness of vaccine receipt as well as the impact of new vaccine introduction on vaccination behavior were used to

adjust models, including household wealth status, ethnicity, and study setting. All analyses were conducted using Stata V16.1 in July of 2020.

Results

From January 2003 to December 2015, the NUHDSS registered 13,563 children one year of age living in Viwandani and Korogocho. Overall, 69.9% of the children who were 12-23 months at the time of interview had a vaccination card available for review at one or more interviews during this period (Figure 4-1). The distribution of characteristics based on inclusion criteria of having a vaccination card was relatively well-balanced between children included (n=9,449) and children excluded (4,114) for the entire 2003-2015 surveillance period, though the proportion of children who had a card available at the time of interview varied year to year (min: 44% in 2010, max: 83% in 2012) and children with vaccination cards available were members of marginally wealthier households (Table 4.2). More children with vaccination cards were members of the Kikuyu ethnic group (26%) than any other ethnicity (Luhya: 19%; Luo:20%; Kamba 19%; Kissii:6%; Other:11%), and an equal proportion of male and female children had vaccination histories recorded in both surveillance sites (Table 4.2).

Vaccination history from 5,341 children was recorded during the analytic period of interest (36% in the pre-introduction era [2007-2010]; 19% in the year of introduction [2011] and 45% in the post-introduction era [2012-2015]). The distribution of demographic factors did not vary substantially across these three periods (Table 3.3) whereas a higher proportion of children were reported as being in the poorest wealth quintile in 2003-2006 period. These years were excluded from further analysis to balance the size of the sample for the before and after periods of PCV introduction. The average age of the index child record was 15-16 months old across the

three time periods. More than one-quarter of children were members of the richest households in the two communities for the same period. Just by showing an immunization card, and therefore likely representing children of families who have access to immunization services, the uptake of vaccination based on documented history or recall at time of interview was predictably high: BCG >98%; DPT1> 97%; DPT2> 94%; and DPT3> 90%. However, the proportion of children covered with OPV and measles varied across the three time periods; and fewer than three-quarters of children were reported as having completed their basic immunization schedule (Table 4.3). Additionally, age-appropriate vaccination coverage for each vaccine, defined as the proportion of children who received each vaccine dose by the recommended age, was low across all vaccines doses and time periods.

Among children who had date verification of vaccination on their immunization cards, many were vaccinated >4 weeks after the recommended age (Table 4.4). From 2007-2015, delayed vaccination as a proportion of all children vaccinated during the period was 13.8% for BCG recommended at birth, 18.2% and 20.8% for DPT3 and OPV3 recommended at 14 weeks, and 54% for Measles recommended at 9 months. With the notable exception of persistent delays in measles vaccination, the overall proportion of delayed vaccination across the schedule declined most years from 2007 to 2015. Delayed vaccination was slightly more common in Korogocho than Viwandani, particularly for DPT and OPV (25% vs 12% for DPT3 and 29% vs 13% for OPV3). Children whose families self-reported as Luhya or Luo ethnicities had higher levels of delays than the majority ethnic group (Kikuyu). The distribution of delays skewed much higher in the poorest households compared to the richest, across all vaccination encounters (Table 4.4). While the prevalence of delays in receipt of BCG, DPT1-3, and OPV1-3 was not homogenous across the stratifying characteristics, delays in receipt of measles vaccine at 9

months was documented consistently in more than 50% of children across sociodemographic strata, besides the slight declines observed for the most recent years included from the surveillance system (48% in 2014 and 38% in 2015). Of note, the median age of children who received delayed vaccination (summarized in Supplemental Table 4.1) did not change substantially over time. A small proportion of children were documented as having received recommended vaccines a year a more after the recommended age (Supplemental Table 4.2).

Controlling for calendar year of the interview, there was a statistically significant lower prevalence of delayed vaccination observed in the sample, comparing delays in the post-introduction period (2012 to 2015) to the pre-introduction period (2007-2010) for doses administered at birth, 6 weeks, 10 weeks and 14 weeks (results not shown). Delays in measles receipt, the last dose recommended in the schedule, showed a significant level change in the prevalence of delay in the years following the introduction of PCV compared to the period during pre-introduction (Prevalence Ratio [PR]: 0.93; 95% Confidence Interval [95CI]: 0.87-0.99). After adjusting for surveillance area, ethnicity and wealth, the prevalence ratio of vaccination delay in the post-introduction era compared to the pre-introduction era was slightly attenuated, though the association suggests lower prevalence of delays in the post-introduction period for BCG, DPT1 and DPT3 (Table 4.5). Dissimilar to the unadjusted model, after adjusting for surveillance area, ethnicity, and wealth, the prevalence of measles vaccine delays was higher in the post-PCV period than the pre-PCV period, though this difference was not statistically significant (Table 4.5).

Discussion

The introduction of PCV, as well as other vaccines such as RV and more recently IPV, Human Papillomavirus Vaccine (HPV) and Malaria vaccine (RTS,S), are important markers of

progress for immunization services and child health in Kenya. However, new vaccine introduction also imposes substantial, long-term financial commitments on ministries of health once vaccines like PCV and RV are adopted for routine use. Evidence that these newly incorporated vaccines do not result in disruption or deterioration of other routine immunization services is paramount in settings that must balance the desire to innovate with the need for continued investment in improving immunization coverage and timeliness overall. In this study, using a quantitative approach, we found that new vaccine introduction was not associated with any significant decreases in the timeliness of routine immunization services in two urban, poor communities in Nairobi.

While our comparative assessment of routine immunization timeliness between the periods before and after PCV introduction were to serve as illustrative of the influence of new vaccine introduction generally, our findings may contribute to the case for sustaining PCV in the routine schedule going forward. Kenya, like many LMICs, introduced new vaccines into the routine schedule with the support of co-financing from Gavi, the Vaccine Alliance, a public-private partnership created to improve access to new and under-utilized vaccines in the world's poorest countries.[2] Gavi's funding agreements are designed to be time bound with a view to 'graduate' country immunization programs from donor support and transition them to a fully self-financed model, using domestic resources to pay for the purchase and delivery of new vaccines. Countries subscribing to this financial model assume the full cost of new vaccines after the 3-year average gross national income per capita (GNIpc) exceeds US$1580.[25] Using GNIpc projections for the current decade, Kenya is slated to complete its transition and become financially responsible for sustaining the inclusion of PCV as soon as 2027 along with other newly adopted vaccines (i.e. RV, IPV) in the KEPI shortly thereafter.[26] The decision to prioritize resources for the continued

use of PCV in the routine schedule may take into account how the new vaccine program fits with the overarching goals of the KEPI to achieve high, on-time coverage of routine vaccines.

Decisions about the introduction of new vaccines into the routine immunization schedule are generally made at the central government level, and the responsibility of rollout is held with local health authorities. It is for this reason that studying the potential systems shocks of changes to the immunization schedule at more localized levels is important for identifying and addressing any challenges, particularly among target children who are at higher risk for premature death due to their living conditions and circumstances.[8,27] To our knowledge, this study is the first to show that following recent new vaccine introduction in a local setting, timeliness of other routine immunization slightly improved, or remained neutral to the presence of additional vaccines in the schedule. Without accompanying qualitative understanding of the reception of new vaccines by the communities residing in Korogocho and Viwandani, we cannot further substantiate the association; and the comparative prevalence ratios may actually capture aggregate average declines in delayed vaccination that initiated well before PCV introduction in 2011. Nonetheless, the fact that we did not observe any substantial spikes or large prevalence ratios comparing delayed vaccination in the preceding and after periods of PCV introduction is evidence to say that the delivery of routine immunization services did not experience disruption or deterioration associated temporally with the incorporation of new vaccines in Korogocho and Viwandani.

Much like findings from previous research on vaccination coverage and completion in Korogocho and Viwandani, our assessment of delayed vaccination over time in the two communities underscores the extent to which children are under-immunized and are at sustained risk of vaccine-preventable diseases. In 2015, fewer than three-quarters of children were complete in their immunization schedules. Another study, with a primary focus on assessing

intervenable differences to close the gap between children with complete and incomplete immunization schedules, found that children who had not completed their schedules by 12 months of age were frequently delayed in one or more doses of their vaccination schedule.[28] With up to 50% of our sample being delayed in their measles vaccination, there undoubtedly is an impact on children completing their schedules and more importantly achieving protection against the VPDs targeted by the KEPI within their most vulnerable year of life before the first birthday.

When compared to estimated delayed vaccination at the national-level, children in Korogocho and Viwandani, had substantially higher levels of delayed measles vaccination, 54% overall for the study period compared to an estimated 28% nationwide in 2014.[29] Delayed vaccination for other routine doses in Korogocho and Viwandani was lower than the national estimates (BCG: 13.8% vs. 24.3%; DPT1: 8.1% vs. 10.6%; DPT2: 12.6% vs. 18.1%; DPT3: 18.2% vs. 24.7%), though there were significant differences in the proportion of delayed vaccination across socioeconomic strata in our study, with the proportion of children delayed in their vaccination being much higher for minority ethnic groups and lower wealth strata. In contrast, delays in measles vaccination persisted across time and social determinants in both communities. This is particularly concerning in an urban, slum setting where vaccine-preventable disease transmission intensity is likely higher, coupled with the influence of migrant effects, other food security and sanitation risks, posing serious challenges for childhood survival.[27]

Evaluating program changes using quantitative methods often suffers from bias due to unobserved confounding and heterogeneity in study samples. This study which compared delays in vaccination receipt between two periods and found a significant reduction in delays for some

vaccines is subject to the same type of methodological concern. Nonetheless, we have not sought to determine causal associations, rather define from an evaluation perspective that there were no large increases in the proportion of children receiving delayed vaccination following the first new vaccine introduction of recent introductions. We were not able to control for additional factors that may have a time-specific association with vaccination timeliness, such as anti-vaccine media campaigns, vaccine supply stock-outs, or supplementary immunization activities. A second important limitation to our study is the exclusion of children who did not have a vaccination card at the time of interview. The proportion of children who had a card available at the time of interview was not stable over time, ranging from 83% in 2012 to 44% in 2010. If children without vaccination cards discarded or lost them upon completing their schedules on-time, then our findings may over-estimate the extent of the risk that delayed vaccination poses to these two communities. However, it is more likely that the lack of a vaccination card represents an access barrier to immunization services and the exclusion of children without cards may under-estimate the true prevalence of delays, or even non-vaccination. A longitudinal surveillance platform like the NUHDSS is a worthwhile investment by governments and donors to ensure that health needs are being met in communities that lack coverage of health services and attention from national-scale death registries. However, the setting in which the NUHDSS operates is a challenge to complete follow-up. The average in-migration for children under-five is 36.9% annually, whereas the average out-migration is 31.4%.[19] This circular migration pattern is an obstacle to obtaining complete immunization records for all births registered in the system and because of this there may be different levels of representation in our sample from year to year.

Conclusion

In two urban, informal settlements, the introduction of new vaccines was not associated with significantly higher prevalence of delayed vaccination in the routine immunization program. With a large concentration of the urban population residing in informal settlements in Nairobi, on-time and up-to-date vaccination is essential for continued progress towards improving childhood health among the most vulnerable. New vaccine introduction might be a used to rejuvenate program goals, increasing coverage to more diseases and improving the uptake and timeliness overall of immunization services.

Table 4.1 Cut-offs for on-time vaccination according to age-specific recommendations in the Kenyan Expanded Programme on Immunization (KEPI)*

Age at administration	Vaccines	Minimum acceptable age (in days)	Delays initiated (age in days)
Birth	BCG, OPV0	0	≥ 31
6 weeks	Penta1, OPV1	42	≥ 72
10 weeks	Penta2, OPV2	Age in days at previous dose + 28	≥ 100
14 weeks	Penta3, OPV3	Age in days at previous dose + 28	≥ 128
9 months	Measles	252	≥ 282

*PCV introduced in 2011 and RV in 2014. Both vaccines are recommended at 6 and 10 weeks, and a third dose at 14 weeks. Not included in the evaluation of timeliness.

Table 4.2 Characteristics of children 12-23 months identified in NUHDSS (2003-2015) according to the availability of a vaccination card

	Overall	Card	Recall
		Frequency (%)	
Total	13,563(100%)	9,449 (100%)	4,114 (100%)
Surveillance site			
Korogocho	6,720 (50%)	4,934 (52%)	1,786 (43%)
Viwandani	6,843 (50%)	4,515 (48%)	2,328 (57%)
Gender			
Male	6,883 (51%)	4,180 (51%)	2,073 (50%)
Female	6,680 (49%)	4,639 (49%)	2,041 (50%)
Ethnicity			
Kikuyu	3,544 (26%)	2,464 (26%)	1,080 (26%)
Luhya	2,464 (18%)	1,755 (19%)	709 (17%)
Luo	2,638 (19%)	1,880 (20%)	758 (18%)
Kamba	2,703 (20%)	1,829 (19%)	874 (21%)
Kissii	766 (6%)	507 (5%)	259 (6%)
Other	1,448 (11%)	1,014 (11%)	434 (11%)
Wealth quintile			
Poorest	2,328 (17%)	1,540 (16%)	788 (19%)
Poor	2,347 (17%)	1,551 (16%)	796 (19%)
Middle	2,568 (19%)	1,766 (19%)	802 (19%)
Rich	3,060 (23%)	2,136 (23%)	924 (22%)
Richest	3,260 (24%)	2,456 (26%)	804 (20%)
Year			
2003	2,155 (16%)	1,338 (14%)	817 (20%)
2004	1,624 (12%)	1,175 (12%)	449 (11%)
2005	1,093 (8%)	751 (8%)	342 (8%)
2006	1,242 (9%)	888 (9%)	354 (9%)
2007	820 (5%)	519 (5%)	301 (7%)
2008	1,142 (9%)	879 (9%)	263 (6%)
2009	709 (3%)	324 (3%)	385 (9%)
2010	511 (2%)	224 (2%)	287 (7%)
2011	1,285 (9%)	1036 (11%)	250 (6%)
2012	1,542 (11%)	1273 (13%)	259 (7%)
2013	916 (7%)	728 (8%)	188 (5%)
2014	521 (4%)	297 (3%)	224 (5%)
2015	237 (2%)	132 (1%)	105 (3%)

Table 4.3 Demographic factors and vaccination status among children 12-23 months registered in the NUHDSS with a vaccination card by time period

	Period excluded (2003-2006)	Period prior to new vaccine intro (2007-2010)	Period during new vaccine intro (2011)	Period after new vaccine intro (2012-2015)
	n = 4108	**n = 1905**	**n = 1031**	**n = 2405**
Age				
in months, mean	15.76	15.72	16.40	15.13
Study site				
Korogocho	56.4%	46.3%	52.3%	49.7%
Viwandani	43.6%	53.7%	47.7%	50.3%
Gender				
Male	50.9%	49.8%	51.7%	51.4%
Female	49.1%	50.2%	48.3%	48.6%
Ethnicity				
Kikuyu	25.9%	27.2%	28.0%	24.7%
Luhya	16.7%	20.1%	18.0%	20.8%
Luo	23.7%	17.6%	17.6%	16.3%
Kamba	17.3%	21.4%	21.0%	20.6%
Kissii	4.5%	6.1%	4.8%	6.5%
Other	12.0%	7.7%	10.7%	11.1%
Wealth quintile				
Poorest	21.3%	14.0%	11.1%	11.8%
Poor	16.2%	16.6%	18.4%	15.8%
Middle	18.1%	18.4%	20.1%	19.3%
Rich	20.8%	23.3%	21.3%	25.7%
Richest	23.6%	27.6%	29.1%	27.5%
Vaccines received*				
BCG	99.8%	99.6%	98.6%	97.3%
DPT1	99.0%	98.5%	97.8%	97.0%
DPT2	97.4%	97.4%	95.2%	94.1%
DPT3	94.8%	94.4%	89.9%	90.7%
OPV1	98.8%	98.3%	96.9%	96.9%

OPV2	96.9%	96.8%	93.3%	93.9%
OPV3	94.0%	94.3%	87.1%	90.9%
Measles	85.9%	85.9%	78.0%	73.8%
All (by 12 months of age)**	76.3%	72.5%	66.3%	62.5%

* based on both recall and card record of vaccination
** "all" or fully immunized child coverage includes only children who had card record for all vaccines as denominator in order to verify receipt by 12 months of age for all vaccines: n=3,030 for excluded period; n = 1,512 for pre-introduction period; n = 958 for year of introduction period; n = 2,262 for post-introduction period

Table 4.4 Prevalence of delayed vaccination in children 12-23 months registered in the NUHDSS before, during and after PCV introduction according to demographic factors

	BCG		DPT1		DPT2		DPT3		OPV1		OPV2		OPV3		Measles	
	% delayed (total frequency)															
Overall delay	13.8%	(5219)	8.1%	(5131)	12.6%	(4962)	18.2%	(4705)	11.4%	(5101)	15.6%	(4917)	20.8%	(4621)	54.0%	(3811)
Study site																
Korogocho	15.3%	(2563)	10.5%	(2494)	17.0%	(2378)	25.0%	(2213)	15.2%	(2470)	21.6%	(2345)	29.3%	(2150)	55.5%	(1691)
Viwandani	12.3%	(2656)	5.7%	(2637)	8.4%	(2584)	12.1%	(2492)	7.8%	(2631)	10.2%	(2572)	13.4%	(2471)	52.8%	(2120)
Gender																
Male	13.6%	(2664)	8.7%	(2611)	13.3%	(2520)	18.7%	(2375)	11.6%	(2587)	15.7%	(2505)	21.1%	(2329)	54.5%	(1935)
Female	13.9%	(2555)	7.4%	(2520)	11.8%	(2442)	17.6%	(2330)	11.1%	(2514)	15.6%	(2412)	20.5%	(2292)	53.5%	(1876)
Ethnicity																
Kikuyu	8.9%	(1369)	5.2%	(1348)	7.5%	(1322)	12.6%	(1265)	9.7%	(1337)	12.6%	(1306)	17.4%	(1240)	51.0%	(1006)
Luhya	20.6%	(1045)	12.3%	(1038)	19.6%	(1001)	26.3%	(947)	15.3%	(1030)	20.9%	(990)	27.5%	(932)	54.8%	(786)
Luo	18.3%	(895)	9.9%	(865)	16.7%	(810)	23.9%	(752)	13.3%	(860)	20.2%	(801)	27.6%	(736)	52.9%	(569)
Kamba	10.3%	(1092)	5.0%	(1080)	7.6%	(1060)	12.1%	(1022)	7.2%	(1077)	9.9%	(1056)	13.6%	(1007)	53.0%	(869)
Kissii	9.1%	(309)	6.2%	(308)	9.5%	(304)	11.6%	(293)	7.8%	(308)	10.9%	(304)	11.5%	(287)	58.8%	(257)
Other	15.1%	(509)	11.6%	(492)	17.8%	(465)	25.4%	(426)	15.3%	(489)	21.3%	(460)	27.7%	(419)	62.0%	(324)
Wealth quintile																
Poorest	17.7%	(651)	11.2%	(633)	15.5%	(612)	21.4%	(579)	14.0%	(637)	18.4%	(609)	25.3%	(570)	54.8%	(473)
Poor	14.9%	(863)	7.9%	(857)	13.7%	(827)	19.5%	(780)	11.4%	(853)	17.2%	(821)	22.6%	(769)	55.4%	(643)
Middle	15.8%	(998)	8.8%	(980)	13.3%	(945)	20.0%	(887)	12.8%	(974)	17.7%	(930)	23.8%	(858)	57.1%	(718)
Rich	11.9%	(1251)	7.8%	(1234)	11.5%	(1194)	16.6%	(1134)	10.6%	(1220)	14.1%	(1186)	18.1%	(1119)	51.9%	(919)
Richest	11.5%	(1456)	6.5%	(1427)	11.0%	(1384)	16.1%	(1325)	9.8%	(1417)	13.4%	(1371)	18.2%	(1305)	52.6%	(1058)
Year																
2007	27.1%	(513)	10.9%	(497)	15.1%	(483)	25.0%	(452)	16.2%	(495)	19.9%	(473)	28.1%	(431)	57.4%	(345)
2008	16.9%	(856)	9.8%	(819)	15.5%	(785)	21.9%	(744)	14.9%	(813)	22.1%	(777)	29.0%	(724)	57.3%	(623)
2009	19.9%	(302)	13.8%	(297)	18.6%	(290)	27.3%	(271)	13.9%	(296)	17.4%	(287)	27.5%	(276)	58.0%	(231)
2010	16.0%	(212)	10.7%	(205)	14.4%	(202)	19.7%	(183)	9.3%	(205)	11.9%	(201)	22.1%	(190)	52.8%	(159)
2011	10.4%	(1011)	6.8%	(1001)	11.7%	(967)	17.6%	(907)	13.1%	(984)	18.4%	(946)	22.7%	(867)	50.6%	(770)
2012	8.4%	(1227)	5.8%	(1229)	9.8%	(1183)	13.6%	(1128)	7.2%	(1223)	10.7%	(1186)	14.3%	(1136)	55.4%	(909)
2013	11.7%	(683)	6.4%	(672)	10.5%	(649)	14.4%	(625)	8.1%	(675)	11.0%	(646)	14.7%	(612)	54.2%	(450)
2014	13.4%	(291)	9.0%	(289)	12.3%	(285)	16.3%	(282)	12.9%	(287)	15.2%	(283)	16.8%	(273)	48.4%	(225)
2015	11.3%	(124)	7.4%	(122)	11.0%	(118)	16.8%	(113)	7.3%	(123)	11.9%	(118)	14.3%	(112)	38.4%	(99)

Children with date on card (denominator)	5219	5131	4962	4705	5101	4917	4621	3811
who received vaccine	5254	5218	5098	4907	5202	5065	4879	4214
who did not receive vaccine	87	123	243	434	139	276	462	1127
Total	5341	5341	5341	5341	5341	5341	5341	5341

Note: percentages for delayed vaccination are row percentages and total frequencies in parentheses are column totals.

Table 4.5 Multivariable associations between time period (2007-2010 versus 2012-2015) and delays in vaccination for doses at birth, 6 weeks, 14 weeks and 9 months of age among children 12-23 months registered in the NUHDSS

	Prevalence ratios (95% CI) ref = on-time vaccination							
	BCG (birth)		**DPT1 (6 weeks)**		**DPT3 (10 weeks)**		**Measles (9 months)**	
Period (ref = pre [2007-2010])								
Post (2012-2015)	0.67	(0.45-0.99)	0.41	(0.24-0.69)	0.59	(0.41-0.83)	1.19	(0.99-1.42)
Surveillance site (ref = Korogocho)								
Viwandani	0.89	(0.86-1.02)	0.64	(0.51-0.80)	0.56	(0.48-0.66)	0.93	(0.086-0.99)
Ethnicity (ref = Kikuyu)								
Luhya	2.21	(1.76-2.78)	2.50	(1.83-3.40)	2.20	(1.79-2.69)	1.06	(0.97-1.17)
Luo	2.04	(1.61-2.58)	1.91	(1.37-2.67)	1.88	(1.51-2.33)	1.00	(0.90-1.12)
Kamba	1.26	(0.96-1.65)	1.30	(0.88-1.92)	1.28	(0.99-1.66)	1.05	(0.95-1.16)
Kissii	1.15	(0.76-1.74)	1.64	(0.95-2.84)	1.35	(0.91-2.01)	1.15	(1.00-1.32)
Other	1.78	(1.32-2.39)	2.32	(1.58-3.40)	2.01	(1.56-2.57)	1.17	(1.04-1.31)
Wealth quintile (ref = poorest)								
Poor	0.86	(0.67-1.10)	0.73	(0.51-1.04)	0.83	(0.66-1.04)	1.02	(0.90-1.14)
Middle	0.85	(0.67-1.08)	0.84	(0.60-1.16)	0.93	(0.75-1.15)	1.06	(0.94-1.18)
Rich	0.76	(0.60-0.96)	0.80	(0.58-1.10)	0.76	(0.61-0.94)	0.97	(0.86-1.08)
Richest	0.68	(0.54-0.87)	0.66	(0.47-0.91)	0.70	(0.57-0.87)	0.94	(0.84-1.05)
Observations	4208		4130		3798		3041	

Table 4.6 Median and outlier (max) ages at vaccination among children who received delayed vaccination

	BCG at birth	OPV1 at 6 weeks	OPV2 at 10 weeks	OPV3 at 14 weeks	DPT1 at 6 weeks	DPT2 at 10 weeks	DPT3 at 14 weeks	Measles at 9 months
	>28 days	**≥72 days**	**≥100 days**	**≥128 days**	**≥72 days**	**≥100 days**	**≥128 days**	**≥282 days**
	n = 719	n = 579	n = 769	n = 961	n = 414	n = 623	n = 854	n = 2058
2007	43 (25)	89 (41)	121 (94)	157 (66)	87 (31)	118 (29)	152 (54)	298 (37)
2008	47 (36)	95 (39)	119 (44)	150 (57)	92 (94)	130 (75)	158 (72)	296 (27)
2009	50.5 (86)	92 (40)	123 (50)	162 (80)	92 (39)	124 (51)	161 (88)	301 (49)
2010	57 (323)	89 (327)	127 (52)	153 (70)	107 (333)	127 (53)	153 (52)	298 (22)
2011	50 (41)	116 (211)	122 (58)	160 (74)	92 (131)	117 (39)	155 (63)	301 (34)
2012	46 (38)	174 (307)	116 (34)	147 (57)	82 (44)	114 (31)	143 (33)	301 (36)
2013	48 (79.5)	141 (330)	124 (114)	155 (62)	129 (328)	131 (114)	150 (50)	299 (28)
2014	69 (330)	244 (331)	113 (82)	149 (69)	108 (331)	118 (271)	149 (76)	298 (29)
2015	64.5 (325)	109 (152)	124 (155)	153 (71)	153 (118)	137 (155)	156 (179)	292 (47)
Overall	**47 (43)**	**91 (66)**	**120 (50)**	**154 (61)**	**93 (106)**	**120 (52)**	**150 (59)**	**296 (26)**

	BCG at birth	OPV1 at 6 weeks	OPV2 at 10 weeks	OPV3 at 14 weeks	DPT1 at 6 weeks	DPT2 at 10 weeks	DPT3 at 14 weeks	Measles at 9 months
	>28 days	**≥72 days**	**≥100 days**	**≥128 days**	**≥72 days**	**≥100 days**	**≥128 days**	**≥282 days**
	n = 719	n = 579	n = 769	n = 961	n = 414	n = 623	n = 854	n = 2058
2007	533	584	614	540	584	614	540	609
2008	511	653	596	625	653	596	625	664
2009	623	661	674	511	661	674	490	656
2010	428	449	463	462	453	449	437	425
2011	690	439	512	544	447	448	512	679
2012	506	538	566	601	538	566	601	644
2013	398	786	575	607	426	575	607	1006
2014	733	1139	469	483	441	471	544	564
2015	707	412	452	487	412	443	487	643

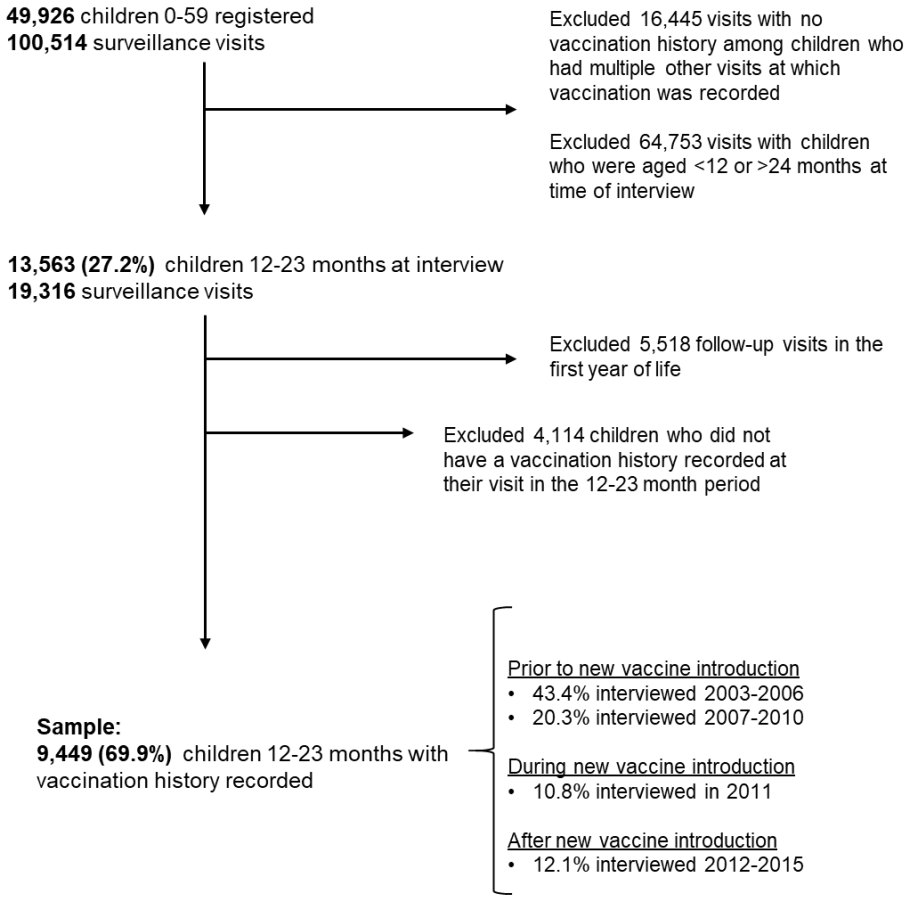

Figure 4-1 Study sample diagram of children 12-23 months registered in NUHDSS from 2003-2015 with vaccination data

References

1. Loharikar A, Dumolard L, Chu S, Hyde T, Goodman T, Mantel C. Status of new vaccine introduction – worldwide, September 2016. *Relev Epidemiol Hebd*. 2017;92(1):1-8. doi:10.15585/mmwr.mm6541a3
2. Gandhi G. Charting the evolution of approaches employed by the Global Alliance for Vaccines and Immunizations (GAVI) to address inequities in access to immunization: A systematic qualitative review of GAVI policies, strategies and resource allocation mechanisms thr. *BMC Public Health*. 2015;15(1). doi:10.1186/s12889-015-2521-8
3. Hyde TB, Dentz H, Wang SA, Burchett HE, Mounier-Jack S, Mantel CF. The impact of new vaccine introduction on immunization and health systems: A review of the published literature and The New Vaccine Introduction Impact Published Literature Working Group 1 HHS Public Access. *Vaccine*. 2012;30(45):6347-6358. doi:10.1016/j.vaccine.2012.08.029.The
4. Mihigo R, Okeibunor J, Anya B, Mkanda P, Zawaira F. Challenges of immunization in the African Region. *Pan Afr Med J*. 2017;27(Supp 3):12. doi:10.11604/pamj.supp.2017.27.3.12127
5. World Health Organization. *Immunisation Agenda 2030: A Global Strategy to Leave No One Behind*.; 2020.
6. Phillips DE, Dieleman JL, Lim SS, Shearer J. Determinants of effective vaccine coverage in low and middle-income countries: A systematic review and interpretive synthesis. *BMC Health Serv Res*. 2017;17(1). doi:10.1186/s12913-017-2626-0
7. Guerra FA. Delays in Immunization Have Potentially Serious Health Consequences. *Pediatr Drugs*. 2007;9(3):143-148.
8. Mutua MK, Mohamed SF, Kimani-Murage EW, et al. Complete and on-time routine childhood immunisation: determinants and association with severe morbidity in urban informal settlements, Nairobi, Kenya. *Ann Hum Biol*. 2020;47(2):132-141. doi:10.1080/03014460.2020.1725121
9. Sambala EZ, Wiyeh AB, Ngcobo N, Machingaidze S, Wiysonge CS. New vaccine introductions in Africa before and during the decade of vaccines – Are we making progress ? *Vaccine*. 2020;37(25):3290-3295. doi:10.1016/j.vaccine.2019.05.002
10. Burchett HED, Mounier-jack S, Torres-rueda S, et al. The impact of introducing new vaccines on the health system : Case studies from six low- and middle-income countries. 2014;32(48):6505-6512. doi:10.1016/j.vaccine.2014.09.031
11. Torres-Rueda S, Burchett HE, Griffiths UK, et al. New pneumococcal conjugate vaccine introductions in four sub-saharan african countries: A cross-country analysis of health systems' impacts. *Afr Health Sci*. 2015;15(3):868-877. doi:10.4314/ahs.v15i3.22
12. de Oliveira LH, Trumbo SP, Ruiz Matus C, Sanwogou NJ, Toscano CM. Pneumococcal conjugate vaccine introduction in Latin America and the Caribbean: progress and lessons learned. *Expert Rev Vaccines*. 2016;15(10):1295-1304.

doi:10.1586/14760584.2016.1166961
13. de Oliveira LH, Toscano CM, Sanwogou NJ, et al. Systematic documentation of new vaccine introduction in selected countries of the Latin American Region. *Vaccine*. 2013;31(SUPPL.3):C114-C122. doi:10.1016/j.vaccine.2013.05.032
14. Shearer JC, Walker DG, Risko N, Levine OS. The impact of new vaccine introduction on the coverage of existing vaccines : A cross-national , multivariable analysis. *Vaccine*. 2012;30(52):7582-7587. doi:10.1016/j.vaccine.2012.10.036
15. Ndiritu M, Cowgill KD, Ismail A, et al. Immunization coverage and risk factors for failure to immunize within the Expanded Programme on Immunization in Kenya after introduction of new Haemophilus influenzae type b and hepatitis b virus antigens. 2006;8:1-8. doi:10.1186/1471-2458-6-132
16. Hull BP, Menzies R, Macartney K, Mcintyre PB. Impact of the introduction of rotavirus vaccine on the timeliness of other scheduled vaccines : The Australian experience ☪. *Vaccine*. 2013;31(15):1964-1969. doi:10.1016/j.vaccine.2013.02.007
17. Zou G, Itik B, Anas L, et al. Effects of the introduction of new vaccines in Guinea-Bissau on vaccine coverage, vaccine timeliness, and child survival: An observational study. *Vaccine*. 2017;9(1):1-12. doi:10.1371/journal.pone.0037905
18. Sadoh AE, Nwaneri DU, Ogboghodo BC, Sadoh WE. Effect of introduction of pentavalent vaccine as replacement for Diphtheria-Tetanus-Pertussis and Hepatitis B vaccines on vaccination uptake in a health facility in Nigeria. *Vaccine*. 2016;34(24):2722-2728. doi:10.1016/j.vaccine.2016.04.026
19. Beguy D, Elung'ata P, Mberu B, et al. Health & Demographic Surveillance System Profile: The Nairobi Urban Health and Demographic Surveillance System (NUHDSS). *Int J Epidemiol*. 2015. doi:10.1093/ije/dyu251
20. Beguy D, Bocquier P, Zulu EM. Circular migration patterns and determinants in Nairobi slum settlements. *Demogr Res*. 2010;23(20):549-586.
21. Emina J, Beguy D, Zulu E, et al. Monitoring of health and demographic outcomes in poor urban settlements: Evidence from the Nairobi Urban Health and Demographic Surveillance System. *J Urban Health*. 2011;88(2):S200-218.
22. M.K. M, E. K-M, R.R. E. Childhood vaccination in informal urban settlements in Nairobi, Kenya: who gets vaccinated? *BMC Public Health*. 2011;11(1):6. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed10&NEWS=N&AN=21205306.
23. Beguy D, Elung'ata P, Mberu B, et al. Health & Demographic Surveillance System Profile: The Nairobi Urban Health and Demographic Surveillance System (NUHDSS). *Int J Epidemiol*. 2015;44(2):462-471. doi:10.1093/ije/dyu251
24. Wamukoya M, Kadengye DT, Iddi S, Chikozho C. The Nairobi Urban Health and Demographic Surveillance of slum dwellers, 2002–2019: Value, processes, and challenges. *Glob Epidemiol*. 2020;2:100024. doi:10.1016/j.gloepi.2020.100024
25. Kallenberg J, Mok W, Newman R, et al. Gavi's transition policy: Moving from development assistance to domestic financing of immunization programs. *Health Aff*.

2016;35(2):250-258. doi:10.1377/hlthaff.2015.1079
26. Ojal J, Griffiths U, Hammitt LL, et al. Sustaining pneumococcal vaccination after transitioning from Gavi support : a modelling and cost-effectiveness study in Kenya. *Lancet Glob Heal*. 7(5):e644-e654. doi:10.1016/S2214-109X(18)30562-X
27. Bocquier P, Beguy D, Zulu EM, Muindi K, Konseiga A, Yé Y. Do migrant children face greater health hazards in slum settlements? evidence from Nairobi, Kenya. *J Urban Heal*. 2011;88(SUPPL. 2):266-281. doi:10.1007/s11524-010-9497-6
28. Mutua MK, Kimani-Murage E, Ngomi N, Ravn H, Mwaniki P, Echoka E. Fully immunized child: Coverage, timing and sequencing of routine immunization in an urban poor settlement in Nairobi, Kenya. *Trop Med Health*. 2016;44(1):1-12. doi:10.1186/s41182-016-0013-x
29. Masters NB, Wagner AL, Carlson BF, Boulton ML. Vaccination timeliness and co-administration among Kenyan children. *Vaccine*. 2018;36(11):1353-1360. doi:10.1016/j.vaccine.2018.02.001

Chapter 5 Discussion and Concluding Reflections

This dissertation examined aspects of immunization completion and timeliness in sub-Saharan Africa, using data from Demographic and Health Surveys in several countries and data from a demographic surveillance site in Nairobi, Kenya. In this chapter, the findings from the three research aims are reviewed in the context of each other and other published literature. Then, the strengths and limitations of the research approach overall, including the methods as well as conceptualization and design of the research itself, are discussed along with proposed future areas of research that merit further inquiry. Finally, this chapter concludes with a summary of implications for immunization programs.

Aims 1 and 2: Using Demographic and Health Surveys to examine matters of immunization timeliness and completion

In aims 1 and 2, DHS data from the same set of sub-Saharan African countries were used to investigate two considerations of immunization performance that have been overlooked in the operational research literature: (1) the relationship between dose-specific delays in the basic immunization series and overall completion rates by 12 months of age; and (2) the relationship between burden of under-five death and vaccination outcomes, defined as being fully immunized with the basic schedule by the time of the interview. Both aims sought to investigate programmatic topics that have implications for concentrating the risk of vaccine-preventable disease transmission and morbimortality.

For the first aim, using only data from children who had vaccination records available at the time of interview, dose-specific delays at any interval in the schedule were associated with substantially lower likelihood of completing the schedule by 12 months of age. The large proportion of children who either received their BCG birth dose late (25%) or delayed the initiation of their three dose series of pentavalent (23%) were the driving force in determining subsequent delays in the series and non-completion by age 12 months. .

Overall, the proportion of children who had not completed their recommended vaccines in their first year of life was 57%, which varied substantially by country from as high as 73% in Gabon to 12% in Burundi. There did not appear to be a threshold at which delays did not matter for completing the schedule across countries. That is, even in countries with fewer children failing to complete their schedules, delays mattered for predicting incompletion rates. It is expected that the relationship between late vaccination and subsequent delays is semi-fixed, owing to the minimal 4 week interval required between vaccination doses to elicit an optimal immune response, effectively maximizing protection.[1] In this sense, our study evidences the programmatic implications of losing children in follow-up, when delays are prolonged and children fail to receive subsequent doses and, as a result, only achieve partial protection against vaccine-preventable diseases.

Delayed vaccination measured as a continuous number of days or weeks that have elapsed since the target age for vaccination has been studied in several populations in sub-Saharan Africa (SSA). These studies have typically sought to estimate the effective coverage at age intervals in weeks or months following the recommended age for vaccination, graphically

depicting the difference in coverage assumed counting any dose administered, irrespective of age at vaccination, and the coverage achieved at each age-specific interval using the inverse Kaplan-Meier survival estimator.[2,3] These age-specific coverage estimates highlight the extent to which children are not protected at the ages targeted by vaccine recommendations – usually the earliest age at which safety and efficacy has been demonstrated in clinical trials. However, examples such as Clark & Anderson 2009 evidenced that many children who were not vaccinated on-time were eventually brought up to date in their schedules in later childhood. These studies overlooked the analytic opportunity to evaluate the dose-specific association of delays with drop-out from the immunization schedule. From a programmatic perspective, identifying the total burden of delayed vaccination in a population and its relationship with driving under-vaccination at 12 months of age is helpful for designing strategies to address the delays that occur at specific dose intervals most frequently, keeping families and their children on-track in their schedules. Periodic intensification of routine immunization (PIRI) through outreach campaigns, carrying children forward in immunization registries until spontaneous demand brings them to health centers, and missing opportunities to offer protection against vaccine-preventable diseases are all implications of delayed vaccination that consume substantial scarce resources for health.

In aim 2, we used birth histories and childhood vaccination data, including maternal recall and card verification, to examine the association between having experienced the death of a child and vaccination outcomes in surviving children among families. We found a weak association between families having experienced the death of a young child and poor vaccination outcomes among subsequent births.. Our guiding hypothesis was that mothers who

experience the premature death of a child under-five would make health choices that favored child survivorship such as immunization. The findings did not support this hypothesis, but it is possible that the hypothesis did not have a clear footing in knowledge regarding behavior change and motivation-driven agency in areas characterized by substantial access disadvantages. Only one other study that we could find in the sub-region, in Nigeria, evaluated the influence of preceding childhood death on subsequent health service utilization patterns among mothers. Though not directly comparable to our outcome measuring vaccination utilization, the authors also found lower likelihood of utilization (postnatal care: OR 0.64, 95%CI 0.57-0.71; skilled birth attendant: OR 0.56; 95%CI 0.50-0.63; postnatal care: OR 0.65, 95%CI 0.55-0.69) in women who experienced the death of a child compared to those who did not. After adjusting for socioeconomic differences, the significance of the relationship did not hold, and the authors concluded there was no association between child death and maternal health service utilization. Their study .

One explanation for the findings in our study and those from the Nigerian study that were not in line with our hypothesis could be that women who experience 100% survivorship of their children, which was used for the index, are not appropriate comparators for evaluating the influence of child death, with so many unobserved or unmeasured confounding factors. Instead, the closest counterfactual for evaluating the relationship between mothers' decisions and motivations to vaccinate their children following exposure to a child death might be comparing survivorship status of births vaccination outcomes among subsequent births within the same mother. That is, among women who have 3 or more births, modelling the per-woman likelihood

of her child being vaccinated following the death of a preceding child's death compared to vaccination outcomes following the the survival of other births. Since the DHS only collects data on vaccination for 3-5 years prior to the survey, the eligible population of women with at least 3 non-multiple births is very small or does not exist in some countries. This, however, could be evaluated using demographic surveillance systems like the NUHDSS because of their ability to longitudinally follow mothers and their children's outcomes.

Most recent research on vaccination describes uptake and timeliness patterns, or evaluates predictors for ensuring both, , as opposed to a focus on under-vaccination and barriers to immunization.[4–6] Yet, strategic goals and plans are often framed around objectives for increasing access to immunization among the 'hard-to-reach' and 'vulnerable' populations. It is generally assumed that children who are under-vaccinated or non-vaccinated are more vulnerable, although this term is poorly defined for program intervention and in research.[7] Scenarios in which under-vaccinated or non-vaccinated children reside in the same geographic area are a substantial challenge for immunization programs. Despite efforts to increase aggregate coverage to high thresholds, under-vaccinated populations that cluster together and have limited interaction with vaccinated populations, have elevated spatial-specific risk for acquiring vaccine-preventable diseases. In this sense, there is a continued need to understand the mechanisms that doubly disadvantage children due to spatial risk of U5M and under-vaccination.

Aims 3: Using the Nairobi Urban Health and Demographic Surveillance System to assess the influence of new vaccine introduction on routine immunization services

In the third aim of this dissertation, the annual prevalence of vaccination delays was evaluated before and after the introduction of PCV in two urban informal settlements in Kenya, Nairobi. Kenya adopted both PCV and RV, vaccines against childhood pneumococcal disease and rotavirus, in the early and mid-2010s. Like many low-middle income countries in the region, Kenya leveraged donor support to subsidize the procurement of these new vaccines and roll them out for routine use. These vaccines were delivered as part of the national immunization program, using the same operational resources and systems available to administer other routine childhood vaccines.[8] We found that there were no significant differences in the average prevalence of delayed vaccination before and after the introduction of PCV in 2011; however, the prevalence of delays in these two communities was persistently high over time and unchanged in the years following new vaccine introduction. Notably, the proportion of children vaccinated by 4 or more weeks late with measles was greater than 50% in most years.

Immunization programs balance the competing priorities of improving coverage and timeliness of routine vaccination while also re-training their workforce to learn new schedules, contraindications, and administration techniques to support the introduction of new vaccines. Our study on the impact of new vaccine introduction for routine services in an urban, poor population underscores that systems were prepared to incorporate new vaccines, at least when co-administered with other doses in the existing schedule, but resources used to invest in new vaccines may have detracted from investment to scale-up coverage and improve the timeliness of vaccination. Other researchers have come to similar conclusions from studying trends in aggregate coverage over time of traditional vaccines in the routine schedule before and after

introduction of new vaccines.[9] Our study is the first to consider any changes to timeliness of vaccination that occurred following the introduction of new vaccines for routine use in a poor, urban area.

A recently published analysis assessed the correlation between levels of donor financing and changes in vaccination coverage across a set of development assistance eligible countries. Consistent with our findings and others, development assistance, including from Gavi – the primary driver of new vaccine introduction in low- and middle-income countries, has not contributed to declines in coverage for traditional vaccines, whereas coverage for new vaccines has substantially improved in these countries during the same time period..[10] New vaccine introduction is often accompanied by investment to expand cold chain systems, develop targeted communication and education about the new antigens, and carry out social mobilization activities. However, these resources from Gavi and other donorsmay not translate to improving the overall outcomes of the immunization system. Going forward, especially as countries prepare to assume more financial responsibility in their cost-sharing agreements[11], considerations for renewed investment in routine services will be needed.

Strengths, limitations, and future directions

Our approach to studying issues of vaccination timeliness differed from approaches used in previous research that were more focused on describing timeliness and coverage. In considering how vaccination timeliness influences or facilitates other program outcomes, such as completion of the basic schedule, we were able to articulate more concrete recommendations for targeting resources or interventions. Nonetheless, the aims in this dissertation that use categorical

classification of vaccination timeliness do so without clear consensus on cut-offs for defining on-time versus delayed vaccination. We considered delayed vaccination as any dose administered 4 weeks or more after the recommended age. Other studies on the timeliness of vaccination in low- and middle-income countries (LMIC) have used lower threshold cut-offs for on-time versus delayed, at 1 or 2 weeks after the recommended age.[12] There clearly is a need for consensus in order to facilitate comparisons across studies; however, more than consensus, defining timeliness based on the underlying known disease mechanisms and implications for vaccine-derived protection associated with late or early vaccination should be more consistently applied. Due to differences in childhood nutritional status, the local epidemiological profile of vaccine-preventable diseases, and the prevalence of breastfeeding across countries, vaccination timeliness may have differing degrees of influence on improving protection against vaccine-preventable diseases between and within countries. For example, the timing of rotavirus vaccination is subject to age-restrictions that reduce the potential risk of adverse outcomes such as intussusception, but there is also evidence that earlier or later vaccination in infancy, depending on the context, might result in better immune responses.[13,14] For future studies, the focus of estimating the health impact and disease implications of delayed vaccination should be prioritized.

In our work, the programmatic definitions used to derive variables on delayed vaccination were used in line with how immunization programs categorize timeliness. However, misclassifying children's vaccination status, either for assessing timeliness, coverage, or completion of the basic schedule, due to recall or reporting errors is a real concern. We

ascertained vaccination status using only review of paper-based records for aims 1 and 3, excluding a sizeable proportion of children who had lost or never had a vaccination card (in aim 1, ~40%). This type of selection bias is a well-recognized data collection and study design challenge in the immunization services research space. Some studies have tried to address this bias by imputing vaccination status for children without cards from the known distribution of values for age at vaccination among children who have cards.[2] However, this approach assumes that children who do not have cards are similar to children who do have cards. Comparing the distribution of covariates in our aim 1, children without cards had mothers who were less educated and poorer in comparison to children with cards, and both of these maternal characteristics were e associated with low vaccination uptake. Due to this limitation, we cannot necessarily generalize findings from studying the timeliness of vaccination in our sample to children who do not have documentation of vaccination. We would anticipate that children without vaccination cards would show higher prevalence of delays and lower overall completion rates, which likely suggests that our estimation of the association between dose-specific delays and overall completion rates is conservative. But we cannot assume that the interval-dependent prevalence of delays would be same between the included and excluded populations due to differences in access to birth delivery in hospitals, among other healthcare use patterns.

Methodological advancements for treating this type of selection bias in the estimation of age-specific vaccination coverage and timeliness is an area for future work. To date, most applications of correcting for selection bias have been employed in higher-income settings using electronic health registry (EHR) data. One example adjusted for incomplete follow-up of the

source population in the Spanish EHR ('Base de datos para la Investigacion Farmacoepidemiologica en Atencia Primaria') using inverse probability weighting methods to generate more precise population-based estimates of Human Papillomavirus (HPV) and pertussis vaccination coverage.[15] Such approaches could be considered for future analyses of the DHS, which do not allow calculation of age at vaccination for children without vaccination cards or children who have died prior to the interview, as we have already discussed.

One important benefit of using data from documented vaccination history in health or vaccine records is that there are other dates in the document that can be used for validity and plausibility inference based on the expected chronological order of event history. The quality of data collected by DHS on vaccination records is generally considered good, and in fact used to grade administrative coverage reports from countries.[16] However, there is always the potential that hurried healthcare workers either do not register dates accurately or fail to register any date of vaccine administration even though it occurred. There is no gold standard comparator for measuring vaccination status, even serological assessment has its drawbacks.[17] Home-based records, such as vaccination cards, and maternal recall have been found to perform consistently well as methods for defining vaccination status.[18]

Another important limitation to this dissertation is the level at which data were compiled and analyzed, which has implications for drawing conclusions and making practical recommendations for immunization programs. First, the scope of aims 1 and 2 included data from a vastly diverse set of countries located in the same sub-region, and representative of different cultural contexts, levels of public health infrastructure, and types of political structures,

all factors that influence the performance of vaccination programs. There were simply too many dimensions that country-level models would have needed to consider to appropriately adjust for each specific context. Instead, we opted to include fixed effect terms for countries in our pooled models to control for unobserved country differences and use the pooled models as a first step in exploring the questions posed in aims 1 and 2.

This approach may have been more suitable for aim 2 than aim 1. In aim 2, we evaluated how the death of a young child in a family might influence vaccination patterns in subsequent children. Although childhood mortality in SSA has declined, the experience of losing a child under-five for mothers and families remains a common event, in terms of the overall proportion being high of women who have had a young child die across their lifetime.[19] In our study, 20% of families (or rather index children) had at least one under-five childhood death in the family occur within the 10 years prior to the survey. Due to the commonality of the event, and one that does not seem to vary substantially across the sub-region[20], it is warranted to explore the relationship between child death within families and their communities and vaccination outcomes using the multi-country pooled approach. In contrast, the study of vaccination timing and completion in aim 1 is highly context dependent and it is considerably more important to account for all contextual differences in attempting to interpret the findings outside of the original intended scope of demonstrating the relationship between timing and completion. For a sensitivity analysis, we estimated country-stratified models to evaluate the association between delays in BCG, penta1, and measles vaccination, respectively, and overall completion. The average associations at country-level were generally consistent with our pooled estimates, but

further investigation into country-specific confounding factors would be needed to develop more appropriate recommendations in targeting resources at the local level. This too could be an area for future work.

There is a second limitation regarding the level, or units, analyzed in this dissertation across all three aims. Using individual children to study vaccination outcomes is preferred to studying aggregate administrative reports that mask heterogeneity in uptake at a more localized level; however, we did not take advantage of the granularity of information available to us in the DHS and NUHDSS to assess the implication of under-vaccination and non-vaccination clustering. It was not an original aim to assess the spatial determinants of timeliness, under-, and non-vaccination in this dissertation, but the use of geocoded data, where available, to evaluate clustered associations between maternal experience with death and vaccination outcomes may have been a more appropriate method to isolate and distinguish between the effects of community and individual-family experiences with childhood death on vaccination patterns for subsequent children. In recent years, DHS and other demographic surveys have made georeferenced data more accessible to the public for use in analysis. Future work to identify where and how under- and non-vaccinated children are geographically distributed within and between lower administrative units across SSA may be an improved indicator for predicting local effective protection from vaccination, as opposed to age-specific coverage.

Implications and significance for public health

The Sustainable Development Goal (SDG) agenda has ambitiously reframed global childhood survival around the goal of reducing under-five deaths to fewer than 25 per 1,000 live

births in every country by 2030.[21] Even though U5M declined by over 50% during the period between 1990-2015, a disproportionate number of childhood deaths still occur in SSA where only 25% of the global infant birth cohort is born, yet 50% of all-cause childhood deaths occur.[22] Expanding the reach of immunization programs will play an important role in continued efforts to reduce preventable child death and morbidity in the sub-region.

Measles vaccination is expected to have the largest impact in continued reduction of the global burden of vaccine-preventable disease, with upwards of 56 million under-five deaths averted between 2000-2030 in 73 of the poorest countries worldwide based on modelling estimation by Gavi's Vaccine Impact Modelling Consortium. Despite evidence that measles vaccination is an essential public health measure for improving child health, especially in rapidly urbanizing areas confronting health transitions, the proportion of children who received measles vaccine late or not at all in our studies was the highest among all vaccinations in the basic schedule. Although not studied in this dissertation, the second dose of measles is available in fewer than 25 countries in the sub-region, as of 2015, increasing the importance of attaining high, on-time coverage with the single dose available to most children.[23]

The role of poor vaccination timeliness and low completion in pooling of risk for vaccine-preventable diseases and potentiating outbreaks associated with poor vaccination patterns clustering geographically is increasing attention in research. In practice, administrative reports, and programmatic knowledge about the distribution of access disadvantages in the community are two important factors that guide the design of outreach, campaign targeting, and social mobilization activities. Using collaboration between researchers and programmatic

decisionmakers, such as is done with the NUHDSS in Nairobi, is important for translating research into improved knowledge and implementation for programs. Strategic goals that have been framed as 'Reaching Every District (RED)' and extending the benefits of vaccination to all children, regardless of place, have been helpful for raising awareness about concerns regarding the accumulation of under- and non-vaccinated children in communities and the impact it has on the dynamics of disease control and overall progress towards expanding the program.[24] However, there is an over-reliance on survey data from the sub-population with vaccination records available to give visualization to issues of timeliness and completion. Although it may not be feasible immediately, continued investment in electronic health information systems, including capture of immunization and other early child health preventive measures, is needed in the sub-region.

Much of this dissertation focused on describing patterns of vaccination in SSA, identifying bottlenecks in delivery, or consideration of disadvantaged groups for prioritized targeting in outreach strategies, using data from 2010-2019 across several countries and settings. There have been several public health emergencies to occur in the sub-region during this same period, but none compare to the current challenges that pandemic spread of SARS-CoV-2 pose for immunization services, as well as other mass distribution public health interventions, in the sub-region.[25] Recent polls from WHO and partners showed substantial disruption in immunization services, citing that 89% of program respondents from the WHO African region are observing diminished demand due to concerns about the risk of exposure to COVID-19, the disease associated with SARS-CoV-2, during vaccination visits in clinical settings, reduced

public transport, or stay-at-home orders.[26] To date, the burden of excess death due to COVID-19 in the sub-region is well below the experience of other regions.[27] Researchers recently predicted that 84 additional childhood deaths (95%CI 14-267) would occur by foregoing immunization services for every excess COVID-19 death prevented due to eliminating additional household exposure to COVID-19 during routine immunization visits.[28] While the benefit of sustaining immunization services exceeds the risks by a sizeable amount, each country and sub-national jurisdiction will need to weigh the tradeoffs between healthcare worker and family exposures to a known risk and the potentially devastating consequences for immunization programs and child health associated with increased numbers of under- and non-vaccinated children. As opportunities present themselves for healthcare workers to engage with communities, catch-ups strategies, especially for outbreak potential VPDs like measles, will need to be prioritized in areas that historically have been behind in their vaccination timeliness and completion due to disadvantages in access.

References

1. Ezeanolue E, Harriman K, Hunter P, Kroger A, Pellegrini C. *General Best Practices Guidance of the Advisory Committee on Immunization Practices (ACIP).*; 2017. www.cdc.gov/vaccines/hcp/acip-recs/general-recs/downloads/general-recs.pdf].
2. Clark A, Sanderson C. Timing of children's vaccinations in 45 low-income and middle-income countries: an analysis of survey data. *Lancet*. 2009;373(9674):1543-1549. doi:10.1016/S0140-6736(09)60317-2
3. Akmatov MK, Mikolajczyk RT. Timeliness of childhood vaccinations in 31 low and middle-income countries. *J Epidemiol Community Heal*. 2012;66(7):e14. doi:10.1136/jech.2010.124651
4. Canavan ME, Sipsma HL, Kassie GM, Bradley EH. Correlates of complete childhood vaccination in East African countries. *PLoS One*. 2014;9(4):e95709. doi:10.1371/journal.pone.0095709
5. Mbengue MAS, Sarr M, Faye A, et al. Determinants of complete immunization among senegalese children aged 12-23 months: Evidence from the demographic and health survey. *BMC Public Health*. 2017;17(1):1-9. doi:10.1186/s12889-017-4493-3
6. Phillips DE, Dieleman JL, Lim SS, Shearer J. Determinants of effective vaccine coverage in low and middle-income countries: A systematic review and interpretive synthesis. *BMC Health Serv Res*. 2017;17(1). doi:10.1186/s12913-017-2626-0
7. Ozawa S, Yemeke TT, Evans DR, Pallas SE, Wallace AS, Lee BY. Defining hard-to-reach populations for vaccination. *Vaccine*. 2019;37(37):5525-5534. doi:10.1016/j.vaccine.2019.06.081
8. Kallenberg J, Mok W, Newman R, et al. Gavi's transition policy: Moving from development assistance to domestic financing of immunization programs. *Health Aff*. 2016;35(2):250-258. doi:10.1377/hlthaff.2015.1079
9. Shearer JC, Walker DG, Risko N, Levine OS. The impact of new vaccine introduction on the coverage of existing vaccines : A cross-national , multivariable analysis. *Vaccine*. 2012;30(52):7582-7587. doi:10.1016/j.vaccine.2012.10.036
10. Ikilezi G, Augusto OJ, Dieleman JL, Sherr K, Lim SS. Effect of donor funding for immunization from Gavi and other development assistance channels on vaccine coverage: Evidence from 120 low and middle income recipient countries. *Vaccine*. 2020;38(3):588-596. doi:10.1016/j.vaccine.2019.10.057
11. Ojal J, Griffiths U, Hammitt LL, et al. Articles Sustaining pneumococcal vaccination after transitioning from Gavi support : a modelling and cost-effectiveness study in Kenya. *Lancet Glob Heal*. 7(5):e644-e654. doi:10.1016/S2214-109X(18)30562-X
12. Masters NB, Wagner AL, Boulton ML. Vaccination timeliness and delay in low- and middle-income countries: a systematic review of the literature, 2007-2017. *Hum Vaccines Immunother*. 2019;15(12):2790-2805. doi:10.1080/21645515.2019.1616503
13. Burke R, Tate J, Pringle K, Patel M, de Oliveira L, Parashar U. Effect of Age at Vaccination on Rotavirus Vaccine Effectiveness in Bolivian Infants. *Pediatr Infect Dis J*. 2019;37(8):1-12. doi:10.1097/INF.0000000000001907.Effect
14. Armah G, Lewis KDC, Cortese MM, et al. A randomized, controlled trial of the impact of alternative dosing schedules on the immune response to human rotavirus vaccine in rural ghanaian infants. *J Infect Dis*. 2016;213(11):1678-1685. doi:10.1093/infdis/jiw023
15. Braeye T, Bauchau V, Sturkenboom M, et al. Estimation of vaccination coverage from

electronic healthcare records; methods performance evaluation – A contribution of the ADVANCE-project. *PLoS One*. 2019;14(9):1-17. doi:10.1371/journal.pone.0222296
16. WHO. *WUENIC Estimates, 2020*.; 2020. https://www.who.int/immunization/monitoring_surveillance/data/en/.
17. Cutts FT, Izurieta HS, Rhoda DA. Measuring Coverage in MNCH: Design, Implementation, and Interpretation Challenges Associated with Tracking Vaccination Coverage Using Household Surveys. *PLoS Med*. 2013;10(5). doi:10.1371/journal.pmed.1001404
18. Dansereau E, Brown D, Stashko L, Danovaro-Holliday MC. A systematic review of the agreement of recall, home-based records, facility records, BCG scar, and serology for ascertaining vaccination status in low and middle-income countries. *Gates Open Res*. 2020;3:1-21. doi:10.12688/gatesopenres.12916.2
19. Sandberg J. Infant Mortality , Social Networks , and Subsequent Fertility Author (s): John Sandberg Published by : American Sociological Association Stable URL : https://www.jstor.org/stable/30038989 Infant Mortality , Social Networks , and Subsequent Fertility. 2006;71(2):288-309.
20. Smith-Greenaway E, Trinitapoli J. Maternal cumulative prevalence measures of child mortality show heavy burden in sub-Saharan Africa. *Proc Natl Acad Sci U S A*. 2020;117(8):4027-4037. doi:10.1073/pnas.1907343117
21. Acheampong M, Ejiofor C, Salinas-Miranda A, Wall B, Yu Q. Priority setting towards achieving under-five mortality target in Africa in context of sustainable development goals: an ordinary least squares (OLS) analysis. *Glob Heal Res Policy*. 2019;4(1):1-16. doi:10.1186/s41256-019-0108-0
22. You D, Hug L, Ejdemyr S, et al. Global, regional, and national levels and trends in under-5 mortality between 1990 and 2015, with scenario-based projections to 2030: A systematic analysis by the un Inter-Agency Group for Child Mortality Estimation. *Lancet*. 2015;386(10010):2275-2286. doi:10.1016/S0140-6736(15)00120-8
23. Masresha B, Luce R, Okeibunor J, Shibeshi M, Kamadjeu R, Fall A. Introduction of The Second Dose of Measles Containing Vaccine in The Childhood Vaccination Programs Within The WHO Africa Region -Lessons Learnt. *J Immunol Sci*. 2018;2(SI1):113-121. doi:10.29245/2578-3009/2018/si.1117
24. The Strategic Advisory Group of Experts (SAGE). *GVAP 2011-2020, Review and Lessons Learned*.; 2020. https://apps.who.int/iris/bitstream/handle/10665/329097/WHO-IVB-19.07-eng.pdf?ua=1.
25. Kapata N, Ihekweazu C, Ntoumi F, Raji T. Is africa prepared for tackling the COVID-19 epidemic. Lessons from past outbreask, ongoing pan-African public health efforts, and implications for the future. *Int J Infect Dis*. 2020;93(January):233-236.
26. Adamu AA, Jalo RI, Habonimana D, Wiysonge CS. COVID-19 and routine childhood immunization in Africa: Leveraging systems thinking and implementation science to improve immunization system performance. *Int J Infect Dis*. 2020;98:161-165. doi:10.1016/j.ijid.2020.06.072
27. WHO. WHO Croonvairus Disease (COVID-19) Dashboard. https://covid19.who.int/. Published 2020.
28. Abbas K, Procter S, van Zandvoort K, et al. Routine childhood immunisation during the COVID-19 pandemic in Africa: a benefit-risk analysis of health benefits versus excess risk of SARS-CoV-2 infection. *Lancet Glob Heal*. 2020;8:e1264-72.

https://doi.org/10.1016/%0AS2214-109X(20)30308-9.